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PULMONARY EMPHYSEMA

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PREFACE

The problems faced by the patient with pulmonary emphysema are at times unusually complex since their treatment may involve the use of a variety of basic medical sciences during the course of his illness. The editors feel fortunate indeed to have as contributors men who have carried out pertinent and timely investigations on the physiologic and therapeutic aspects of the disease described by them. Medical research is characterized not only by advances in knowledge but by retreats in previously held opinions, a circumstance that is responsible for some variation in interpretation of the pathophysiology and treatment of pulmonary emphysema. However, no serious difference in point of view appears to have developed among the contributors, differences of opinion in the literature on this clinical entity have been clearly stated.

The medical management of pulmonary emphysema, as it is carried out in their clinic at Presbyterian Hospital by the editors and Dr Gustav J Beck, will be first presented in order to provide a consistent program of treatment. Reduplication of some material appeared to be necessary to permit the point of view of the individual writer to be adequately expressed with reference to his special topic.

Among our special objectives has been an attempt to establish the continuous inhalation of oxygen as among the most valuable of the agents available for the treatment of pulmonary emphysema, especially when an exacerbation of hypoxia has been precipitated by infection or cardiac insufficiency. Because abrupt administration of relatively high oxygen mixtures has resulted at times in patients becoming comatose, oxygen has been withheld in some clinics even in the presence of serious acute hypoxia. However, significant CO_2 acidosis develops infrequently from a program in which a graded increase in oxygen concentration of the inspired air is carried out unless drugs which depress the respiration have also been used. Intermittent pressure breathing, which in our opinion does not restore cardio-respiratory compensation

as effectively as continuous oxygen therapy, is employed to combat hypoventilation when indicated

Intermittent pressure breathing is advocated as a procedure for those clinical disorders in which it seemed to the editors and their contributors to correct a pathophysiologic state, however, the claims made for it as a routine treatment for pulmonary emphysema have not been supported by the various studies presented in this volume The functional pathology of the bronchi and pulmonary parenchyma in this disease is at times reversible by the use of procedures which may effectively restore cardiorespiratory function and in this way result in improved exchange of oxygen and carbon dioxide between the lungs and arterial blood, and consequently a decrease in CO_2 retention. These measures include oxygen inhalation, antibiotic and prednisone therapy, restoration of diaphragmatic respiration, breathing and postural exercises, alleviation of bronchial obstruction, the employment of bronchodilator and expectorant drugs, enhancement of bronchial drainage, the avoidance of undue hyperventilation as a result of improperly regulated exertion and psychosomatic influences, and the employment of mechanically induced hyperventilation in the treatment of respiratory acidosis, revealed by acid shift in pH

Since the pulmonary bellows is restricted in diffuse obstructive pulmonary emphysema, therapeutic measures which decrease the ventilation as a consequence of providing more efficient gas exchange have been emphasized as of primary importance, in order to relieve dyspnea, prevent alveolar overdistention and increasing bullous disease The test of the volume of ventilation when the patient breathes air as compared to 100 per cent oxygen has, in our experience, appeared to be, in many cases of emphysema, a valuable method of evaluating the progress of the disease as well as the results of therapy The oxygen exercise program to improve general physical fitness as well as cardiopulmonary reserve is an example of a therapeutic procedure that may be tested in this way The characteristic response of other tests of respiratory function are reviewed. The application of respiratory physiology

to the management of various aspects of the disease have been outlined by our various contributors

In addition to the emphasis on the role of oxygen in pulmonary emphysema the reader will find a considerable discussion of CO_2 retention and its significance A difference in point of view has been expressed since some investigators consider carbon dioxide retention as an unmitigated evil whereas the Editors have long been impressed by the benefits of the adaptive mechanism that develops during controlled oxygen therapy whereby increased concentrations of carbon dioxide are eliminated at a lower unit volume of breathing, this has been made clear by the spontaneous lowering of arterial CO_2 tension during the course of oxygen therapy and as result of the improvement in respiratory function produced by inhalation of oxygen An interesting comparison was made of the dyspnea which takes place when mountain climbers return to sea level, their level of bicarbonate, reduced by hyperventilation at high altitudes, is insufficient to compensate for their accustomed CO_2 production for about a week, *i e*, until their base has been restored to a higher level

ALVAN L BARACH
HYLAN A BICKERMAN

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Chapter 1

PATHOGENETIC AND ALLIED INFLUENCES IN CHRONIC PULMONARY EMPHYSEMA

ALVAN L. BARACH, M.D.

INTRODUCTION

Pulmonary emphysema means inflation of the lungs. The term is generally used to describe a chronic disease which in its fully evolved state is readily recognized as a characteristic clinical entity; it has been called hypertrophic or vesicular emphysema to call attention to the progressive distention and rupture of the alveoli, and chronic obstructive emphysema to emphasize the importance of bronchial constriction as a major cause of the clinical symptomatology. Other forms of pulmonary emphysema have been described, such as acute physiologic emphysema, a condition in which hyperinflation of the lungs takes place as a result of severe physical exercise; acute vesicular emphysema in which temporarily overdistention of the alveoli occurs as a result of bronchial obstruction, either localized, as from foreign bodies and tumors, or generalized, as in protracted bronchial asthma.

Senile emphysema is not characterized by over-inflation of the alveoli. Landis states, "In the strict sense of the word this is not a true emphysema at all. It is but one of the atrophic changes commonly met with in the aged." In Laennec's classical description of emphysema, senile emphysema was not included. The hypertrophic obstructive entity with which this volume is concerned is characterized by increased lung volume, impairment of elastic recoil, bronchial obstruction and inefficient alveolar ventilation, in contrast to the tendency to decreased lung volume,

comparatively slight reduction in elastic recoil and unobstructed bronchi in the atrophic, so-called senile emphysema Although senile emphysema is more fully discussed by Bickerman (Chapter 4), I wish to emphasize that the cause of shortness of breath is not simply related to the loss of vital capacity, the moderate impairment of elasticity of the lungs, the decrease of the alveolar breathing surface, or impairment of diffusion, but, as reported by Rappaport and Mayer, is caused by the progressive decline in physical activity In fact, the latter authors, believing that functional disuse is the most important factor in the pathogenesis of emphysema, state " . the involutional lung defect present both in chronic pulmonary emphysema and in senile emphysema is the result of progressive disuse of the organism and hence is functional in its origin as well as in its nature." Whether a developmental so-called "involutional lung defect" is or is not involved in the pathogenesis of chronic pulmonary and senile emphysema, it is becoming steadily more clear that decrease in physical fitness plays a markedly important role in aggravating the symptoms of both diseases Constant physical training is required to maintain the pulmonary reserve of normal individuals at its peak capacity Consideration will be given later to the restoration of respiratory function in patients with pulmonary emphysema who perform daily exercises during the inhalation of oxygen, and thereby undergo a physical training program not possible for them to achieve when breathing air

Monroe, in an extensive clinical and pathologic study of individuals over 61 years of age, emphasized the disagreement between the clinical and pathologic diagnosis in respect to pulmonary emphysema. He stated, "Finally, an important cause of breathlessness during and shortly after effort is merely physical unfitness It is difficult to guess its frequency in this group from hospital records, but the experience of the Geriatric Clinic and the practice outside the hospital is that it is common " Of 129 autopsies in his study the clinical diagnosis of emphysema was omitted from the pathologic summary or stated to be insignificant in 110 cases or 85 per cent, however, in 11 per cent, or 14 cases, advanced emphysema was found postmortem but the clinical

diagnosis had not been made Richards states that chronic pulmonary emphysema of significant anatomical extent is found in about 5 per cent of all autopsies Schlesinger, reporting on aged patients, said that in 666 autopsies evidence of marked emphysema was present in one-third and definite evidence of some emphysema in fully one-half, this series included hypertrophic and atrophic pulmonary emphysema in equal proportions The increasing prevalence of pulmonary emphysema may be explained by better methods of diagnosis and by increased longevity of both men and women Amberson summarized the situation as follows "Practically all aging people develop some degree of pulmonary emphysema and frequently there are changes such as pulmonary fibrosis, chronic adhesive pleurisy and chronic bronchitis Dyspnea is the most common symptom and is the mechanism whereby ventilation of the lungs is maintained as nearly as possible at normal levels It is the cause of the physical limitation and tendency to fatigue which these people experience If ventilation of the lungs and gas exchange cannot be maintained at the physiologic level, chronic anoxia results This aggravates the symptoms mentioned and may result in irritability, weakness, anorexia and impairment in general tone and nutrition Susceptibility to respiratory infection is greater in the emphysematous than in healthy people "

Since the brain is the organ most sensitive to lack of oxygen the fact that hypoxia, either at rest or on exertion, is more common in pulmonary emphysema than in any other chronic ailment justifies the discussion which will appear later in this book on the consequences of hypoxia on mental function Mueller-Deham states "In all old people emphysema is one of the chief agents in lowered physical capacity and the deterioration of the latter is in direct ratio to the severity of the emphysema " The importance of maintaining body tone and pulmonary reserve by cultivating suitable physical exertions, by breathing exercises, and by a suitable oxygen exercise program is emphasized because these considerations apply to people in the middle age as well as in the older age group

Pathogenesis of Pulmonary Emphysema

The pathogenesis of pulmonary emphysema is obscure in most instances It occurs four to five times more commonly in men than in women The writer has observed a number of cases which followed two to six months after an attack of atypical pneumonitis Exposure to certain dusts produces pulmonary fibrosis which is frequently accompanied by some degree of pulmonary emphysema. Other conditions in which a high incidence of the illness is found include chronic pulmonary infection, bronchial asthma, chest deformities, bronchiectasis, pulmonary arteriosclerosis and chronic bronchitis The atrophic changes, associated with loss of vascularity of the alveoli and dissolution of the alveolar walls, may be in part caused by a primary ischemia, an obliterative endarteritis, or these changes in themselves may represent a primary degenerative phenomenon with the vascular changes secondary

Conditions which produce sustained hyperinflation of the alveoli are to be considered as predisposing causes, especially in the presence of a pulmonary parenchyma that is impaired as a result of infection, circulatory abnormalities or constitutional predisposition

The increased intrathoracic pressure developed to overcome resistance to the flow of air, especially during rapid breathing and cough, may result in undue strain on alveolar walls not supported by the opposing pressure of the thoracic cage, namely in the apical regions Trapping of air in dilated alveoli leads to their progressive distention when premature bronchial closure cuts off the expiratory stream of air, especially under circumstances in which bronchial constriction is enhanced because of inflammation of the mucous membranes, presence of occluding exudate in the bronchi, or increased tonus of the bronchiolar muscles, the latter's effect being exaggerated by diminution of the recoiling tension of lung parenchyma which in normal individuals tend to keep the bronchi open This pathophysiologic influence is discussed in Chapter 9 by Daymon and Chapter 11 by Alexander.

Stretching of the lungs at the periphery of the chest during violent inspiratory efforts is probably a major factor in tearing of the alveoli and formation of bullae Due to the characteristic overinflation of the lung, the flattened diaphragm pulls the lower thorax inward, the last five intercostals being apparently not sufficiently forceful to expand the costal margins under these circumstances Aeration of the lower lobes and the hilum is thus impaired and ventilation is then carried on by expansion of the upper thorax which is pulled upward and forward by the upper five intercostal and the accessory muscles of respiration The force of this type of chest expansion, experienced on the alveoli nearest to the point of volume change, appears to exert a damaging influence

Cogent as the above reasoning appears to be, it does not explain the frequent finding of bullous formation in the lower lobes of the lung Perhaps other factors are operative here, such as an increased tendency to bronchial obstruction and infection due to the stagnation of secretions in the dependent parts of the lungs In addition, areas of the pulmonary parenchyma deprived of adequate ventilation may also be secondarily subject to chronic impairment in circulation with resultant atrophic changes It is embarrassing to rigid adherents to the inspiratory theory of alveolar stretching and tearing during lung inflation to explain the presence of a markedly emphysematous lower lobe which, indeed, is little moved by either the diaphragm or lower ribs, even though similar reasoning seems applicable to the periphery of the lung near the upper half of the chest

It is noteworthy that the parenchyma of the lung near the hilum frequently contains well-preserved alveoli that are also perfused with blood As will be commented upon more than once in this volume, the value of restoration of diaphragmatic function, even when of limited degree, is dependent upon the resultant ventilation of the hilum, at the expense fortunately of wasteful disposition of air to bullous areas where respiratory exchange is notoriously inefficient Emphasis shall, therefore, be placed on selective rather than simply the total pulmonary ventilation Liebow has

recently emphasized that renewed considerations should be given to the expanded venous shunts between the right and left sides of the heart as well as to the increased bronchial arterial circulation and the anastomoses of the two arterial systems in pulmonary emphysema The bronchopulmonary venous circulation was found to be greatly expanded in his studies. In regions of the lung in which the pulmonary veins are shut off, the blood may be shunted into the bronchopulmonary veins Although the direction of flow is probably from the left to the right auricle the valves of azygos and the bronchopulmonary veins may lose their competency in advanced emphysema and the flow then be reversed. As a result of the obliteration of the pulmonary arterial and capillary blood the bronchial arterial system becomes immensely expanded with large precapillary anastomoses appearing between the two arterial circulations and with a high pressure systemic circulation in direct communication with the low pressure pulmonary circulation Unsaturated blood from the pulmonary artery may by-pass the diseased parenchyma to considerable extent These communications in addition represent points of resistance that may play a role in the development of arterial hypertension

The small blood vessels of the lungs are not subjected to the normal variations in intrapleural pulmonary emphysema, which tends to impair the flow of blood into the pulmonary venules rather than the bronchial veins, that ordinarily occurs during each inspiration It has also been emphasized by Loeschcke and confirmed by Liebow that the bullae of severe emphysema are in fact expanded parts of the bronchial tree more proximal than the alveoli, including the respiratory bronchioles and bronchioles themselves The musculature surrounding these structures is often markedly hypertrophied The drainage of these structures is by way of the bronchopulmonary veins which, placed within the walls of relatively rigid bronchi, may well be less affected by changes in intrapulmonary pressure. Liebow has acknowledged that the quantitative factors of blood flow in the lungs of patients with chronic pulmonary emphysema and pulmonary fibrosis are admittedly difficult to analyze, but he mentions the interesting fact that in experimental dogs ligation of the pulmonary artery

results in a collateral flow approximately one-third of the right cardiac output

Chronic bronchitis is the most frequently associated condition In a small number of cases an infectious process may be demonstrated by the presence of pus in the sputum, with or without local or generalized bronchiectasis In the larger number of cases the expectoration is mucoid and scant In those instances in which bronchial asthma is also present, the sputum is more viscid and the cough more frequently accompanied by wheezing and difficult respiration, especially in attacks of a paroxysmal nature, rather than by a more or less continuous bronchospasm with periods of relief induced by bronchodilator agents

In patients in whom the factor of paroxysmal bronchospasm is conspicuous, an allergic etiology may be responsible for increasing the severity of the disease In fact, there are instances in which the primary diagnosis, bronchial asthma or pulmonary emphysema, is difficult to make since manifestations of both conditions are clearly evident In such cases, a careful search for extrinsic factors to which the patient may be hypersensitive is indicated Since bronchial asthma does occur in patients with pulmonary emphysema, the elimination of irritant inhalants, revealed by clinical history or skin tests to produce bronchospasm, will manifestly reduce bronchial constriction and alveolar overdistention Desensitization procedures in this group, including the use of pollen, dust and bacterial antigens, may have an effect similar to that achieved by their administration to patients with uncomplicated bronchial asthma, but, in the more commonly encountered case in which prolonged bronchial constriction plays an important role but in which the symptoms of paroxysmal bronchial asthma are absent, the existence of an allergic diathesis, as cause of the production of the mucoid expectoration and bronchospasm, is indeed difficult to demonstrate

If the point of view that bronchospasm itself constitutes an indication of allergy is accepted, then, of course, the condition would be interpreted as allergic in origin The results, however, of investigations from an allergic point of view are generally negative in most patients with diffuse obstructive emphysema,

the skin tests reveal no significant reactions and the clinical history does not as a rule provide a clue to hypersensitiveness to those agents that are admittedly found in younger patients with uncomplicated bronchial asthma In older asthmatic people, the condition is frequently accounted for on the basis of bacterial allergy, in the absence of the findings of extrinsic factors, and treatment of the patient consists of attempts to decrease the hypersensitiveness to bacteria by increasing doses of vaccines made from pyogenic micro-organisms and, generally, by the joint use of house dust as well This approach, however, has not been advocated for the patient with chronic pulmonary emphysema, unless, as stated above, he suffers in addition from bronchial asthma and a suitable investigation has resulted in the finding of a clearly demonstrated allergic factor.

The pathogenesis of the disease may, in time, become more clear by projected studies on the remarkable relation of respiratory infection to an exacerbation in the symptoms of the disease Following a common cold or a viral pneumonitis, a prolonged period of increased dyspnea is characteristic, even in cases in which pyogenic infection does not take place It seems difficult to ascribe this reaction simply to bacterial allergy. In any event, other influences are actively involved which impair respiratory function in addition to the increase in bronchospasm Inflammatory swelling of the bronchiolar mucous membrane, as a result of virus infection or subsequent pyogenic invasion, undoubtedly results in a further increase in constriction of the smaller air passages The increased exudate itself, at first mucoid and, at times, later purulent, adds another factor in the production of obstructive dyspnea The elastic recoil of the pulmonary parenchyma which tends to keep the smaller bronchi patent in expiration may itself be damaged by infection The ventilation becomes less efficient, hypoxia tends to be aggravated, and an increased strain on the circulation may play a role in some cases, especially in the patient group discussed by Richards and Fishman in which cardiac insufficiency became evident

Physiologic studies have made it abundantly clear that any process which increases the degree of bronchiolar constriction

enhances alveolar overdistention, with progressive impairment of respiratory function as revealed in the chapters by Daymon (Chapt 9), Fowler et al (Chapt 10), Levine (Chapt 8) and Bickerman (Chapts 4, 5, 6) Concerning the allergic aspects involved in the pathogenesis of pulmonary emphysema a summary statement may be made that, where suitable evidence has resulted in a clear cause and effect relationship between an extrinsic allergen and the production of bronchospasm, the therapeutic approach should include the use of such knowledge as the allergist may make available However, the fact that the symptomatology of pulmonary emphysema is made worse by upper respiratory infections should not be considered as evidence that the presently employed desensitization programs are effective in decreasing the state of so-called bacterial allergy It is generally agreed that food rarely plays a role in the production of an allergic state, in so far as it may be reliably revealed by skin tests In those instances in which bronchospasm consistently follows the ingestion of a food the patient is generally aware of it

That posture is involved in the pathogenesis of chronic pulmonary emphysema has been maintained by Heckscher who, after reviewing the older literature, emphasized that the erect soldier position is responsible for keeping the lungs in a more inspiratory and hence more constantly inflated state, the vital capacity was found to be decreased and the residual air increased, even in normal men, when the subject moved from an easy standing to an erect lordotic position In other discussions on senile emphysema the mechanism of production of the disease has been attributed to a different change in posture, *i e*, one caused by a degeneration of the intervertebral discs of the dorsal spine, manifested at first by swelling and later by collapse with destruction of the cartilage In this so-called postural emphysema the anteroposterior diameter of the thorax is increased, which gives it a barreling appearance, but impairment of respiratory function is not considered to take place unless the condition is accompanied by obesity Under the latter circumstance, Kerr described the production of dyspnea, defective pulmonary ventilation and, in some instances, subsequent cardiac failure With increase in

obesity, the weight of the abdomen moves the line of gravity forward in the erect posture and, as a compensation for this, the *major portion of the dorsal spine is moved backward and the* thoracic curve becomes exaggerated A barrel-shaped chest occurs as a result of the increased thoracic curve and the diaphragm is pulled downward by the increased weight of the abdominal viscera The poor excursion of the diaphragm lowers the vital capacity and the tidal air, which results in shortness of breath in the standing position referred to by Kerr as "orthostatic dyspnea"

The increased lordosis of the dorsal spine produced by military training, in which the shoulders are drawn backward and the guts sucked, results, according to Heckscher in a tightening of the abdomen and impairment of a diaphragmatic descent, with consequent overinflation of the alveoli The erect standing position does indeed increase the severity of dyspnea in the patient with pulmonary emphysema Patients with pulmonary emphysema breathe better leaning far forward or even walking on all four extremities Sometimes these patients are seen to squat with the lower abdomen pressed against the thighs which, in itself, raises the diaphragm Alexander and Kountz pointed out that exerting pressure with the flat of the hand just above the symphysis pubis, or by a properly designed belt, raised the diaphragm to its normal position of relaxation and in that way restored a certain amount of diaphragmatic respiration It is clear that in the erect military posture the viscera exert a downward pressure on the diaphragm which is a handicap when there is impairment of elastic recoil of the lungs As the patient either sits or walks in the bending forward position, the gravitational force of organs attached to the diaphragm opposing its ascent during expiration is diminished The relaxation pressure of the lungs is further enhanced as *the patient moves from the head up to the head down* position, as will be discussed by Beck (Chapter 7) and the writer (Chapters 2, 3) in subsequent chapters

I have outlined some of the factors in the pathogenesis, or at any rate in aggravation of the symptoms of chronic pulmonary emphysema Our colleagues will present their specialized knowl-

edge concerning a variety of basic sciences frequently involved in this syndrome as well as, it is hoped, information that may be used in the treatment of the individual patient A certain amount of overlapping of material is inevitable since this clinical entity will be presented from various physiologic and therapeutic aspects and because expression of different points of view is intended An account of pulmonary emphysema by one writer would undoubtedly have resulted in a more harmonious picture of the mechanism and therapy of the disease, but at the present state of our knowledge a uniform picture might well be misleading Although recent studies on the physiologic aspects of respiration and circulation have resulted in a number of clinical applications in medical practice, the interpretation of the precise mechanism responsible for improvement has resulted in considerable difference of opinion

The increase in the use of corticotropin, cortisone and, recently, prednisone has resulted in a more powerful control of bronchospasm than was available with the agents previously employed, but at the cost of hazards not formerly present with the employment of conventional bronchodilator agents A similar situation has taken place with the advent of more powerful antibiotic agents in the control of chronic infection

I have said nothing up to this point concerning the effect of emotional influences in respect to the pathogenesis or even modification of the severity of the disease Although no one could stretch his imagination to the point of thinking of pulmonary emphysema as a psychosomatic illness, in the sense that one might conceive of irritable colon or nervous indigestion, it is now clear that certain forms of hyperventilation result in trapping of air in alveoli and overdistention of the lungs There is also evidence that certain emotional states precipitate bronchospasm The occurrence of anxiety as a mechanism productive of an injuriously heightened pulmonary ventilation and consequent overinflation of the lungs, with impaired respiratory function, seems to the writer unquestionable in some cases On the other hand, certain pleasurable forms of excitement and exercise, even when accompanied by hyperventilation, have consequences that appear

more beneficial than a too pastoral life Schutz, in a paper recommending muscular exercise in patients with bronchial asthma, called attention to the observations of Selye on the therapeutic effect of muscular exercise in respect to its stimulating effect on the adrenal cortex, as well as the desirability of a certain amount of adventure, capable of arousing "therapeutically optimal alarming stimuli" The adrenal glands of the domesticated Norway rat were found by Richter to have undergone a marked atrophy during the process of domestication and presumably were less able to protect the animal against hazard and stress than those who lived in their natural environment of peril. I have quoted in this connection the statement of Marlow: "Oft have I surmised, and finally have I learned that Peril is the chiefest way to happiness"

The emotional problems of the patient with pulmonary emphysema are those of man in general, plus the fact that his breathing difficulties pose a continuous threat to his health and comfort The factors involved are too complex to warrant even a summary statement, but it is nonetheless important to realize that a special problem exists Any clinician who sees a number of these patients is entitled to his own opinion, it is probably true that his notion of what an individual patient should or should not attempt, in his extra-medical life, will be based more on his own psychology than on an unbiased estimate of the organic illness and its limitations It has been said that an alcoholic is a man who drinks more than his own doctor I, too, claim no freedom from bias, but I cannot, nonetheless, end this chapter without expressing my own conviction concerning the pathogenetic influences that may affect him, for better or for worse, in this sociopsychological field, apart from the control which the physician exercises in terms of medication and prescribed physical procedures

I am of the belief that a program generally dedicated to physical and mental rest is fraught with hazard! Muscular atrophy, bodily unfitness, and loss of pulmonary reserve are the result of an unwarranted reduction of physical exertion Increasing tension anxiety, hyperventilation and perhaps bronchospasm may be th

consequences of inadequate provision for mental excitement and emotional release Measures which have as their purpose an expansion of the life of the patient, as much as may be feasible, is to my mind a proper objective Too much should not be promised when the disease is well advanced since the response to treatment often leaves much to be desired However, in many cases an improvement of respiratory function may take place at a critical level and the degree of benefit obtained may yield these patients years of useful living As a result of advances in many fields of medicine that have applications to the patient with early or moderately advanced forms of this disease, a good deal of reversible pathology may be overcome It is for this group of partially restored cases that we should encourage as wide a participation in such stimulating activities as his local society and his personality permit, not simply because he deserves to live fully as a human being but also because constricting his activities for the sake of "conserving his energies" leads to psychosomatic disturbances that, in my view, impair respiratory function itself The heart of the matter is the physician's attitude The complexity of the effects of exertion and hyperventilation on the physiologic function of the lungs represents a challenge to our best efforts The factors which govern the decisions faced both by the physician and the patient will be presented in the following pages, in the hope that some additional insight will be provided, not for blanket solutions but for progress toward therapy of the individual patient with pulmonary emphysema

No organized psychoanalytic investigation has been made on patients with pulmonary emphysema but emotional factors may not only play a role in the etiology of asthmatic dyspnea but also it would appear that a specific emotional situation is found in patients with bronchial asthma Since bronchospasm of allergic origin is at times found in emphysema it has seemed of interest to review briefly the investigations of the Chicago School for Psychoanalysis Federn and Weiss suggested that the asthmatic attack is a reaction to the danger of separation from the mother or loss of the mother's love. French summarized his conclusions

as follows: "Asthmatic attacks tend to be precipitated by situations that threaten to separate the patient from some mother figure The separation fear may be actual physical separation; more frequently it is the danger of estrangement from the parental figure due to some temptation to which the patient is exposed In such a situation the asthma attack seems to have the significance of a suppressed cry The infant's cry is at first a physiologic response whose function is the establishment of breathing at birth Very soon it acquires also a psychological meaning as a reaction of helplessness in the face of needs which the infant is unable to satisfy After a time the infant learns that crying brings the mother and the cry becomes then a secondary means to bring the comforting mother to his side. Thus, the primary psychological meaning of crying is a reaction to helplessness in the face of an overwhelming mass of excitation which the ego is powerless to master Fear of losing the mother, however, is a motive that is by no means specific for asthma, is in fact one of the most potent motives leading to the repression of the oedipus complex, especially in girls and in the sons of sexually repressed mothers. . It is, of course, highly probable that the answer to these questions will be found in part upon hereditary emotional patterns in these patients which we might expect to be intimately associated with the hereditary predisposition of these patients to allergic hypersensitivity."

Franz Alexander who participated in this series of investigaions has expressed a similar attitude: "The question arises whether or not individuals, who later are likely to develop asthma, may have a constitutional peculiarity manifesting itself in the difficulty of separation from the mother organism first biologically and later in an emotional sense " The asthma attack is therefore an expression of a protest against separation, that is to say against securing the needed oxygen independently by breathing, and corresponds to a regressive attachment to the mother In some asthma patients the childish habit of breath-holding is also found I have described in a psychoanalytic novel the case history of a man who stammered, in which a regressive attachment to the mother was at the root of his special kind of

breath-holding during stammering * Alexander is fully aware of the speculative nature of these considerations but does produce evidence to suggest that the threshold for allergic sensitiveness is dependent upon the emotional state of the patient In a review of their therapeutic results by George Wilson of 19 psychoanalytically treated patients, 9 became symptom-free, 8 were much improved and 2 were unchanged at the time of the report These therapeutic results were not considered to be indicative of final proof of their hypothesis since not sufficient time had elapsed following completion of treatment The author has observed one patient with pulmonary emphysema in whom psychoanalytic therapy was responsible apparently for a surprising degree of clinical benefit, an outstanding result appeared to be a decreasing need for bronchodilator aerosols, as if the bronchiolar tonus of the hypertrophied bronchial muscles was lessened, plus the fact that the patient rarely allowed herself hyperventilation as a manifestation of tension In fact, the volume of breathing when walking seemed less than that formerly provoked by anxiety Although the therapeutic results of psychotherapy in this disease are difficult to appraise, and admittedly appear of less significance than the immediate problem of symptomatic relief, the writer believes that one should preserve an open mind concerning the question of its use in interested patients to whom this approach is feasible

A selective bibliography is given on page 234

* *The Spectacle of a Man*, by John Coignard Duell, Sloane and Pearce, New York 1937, 1941

Chapter 2

THE APPLICATION OF RESPIRATORY PHYSIOLOGY TO THERAPEUTIC PROCEDURES IN PULMONARY EMPHYSEMA

ALVAN L BARACH, M D

INTRODUCTION

The administration of oxygen is employed *in patients with* pulmonary emphysema for the treatment of impaired respiratory *function due to alveolar overdistention and bronchial* constriction, cardiac insufficiency associated with failure of the right or left heart or both, and decreased pulmonary reserve associated *with loss of physical fitness; oxygen is used intermittently in the* latter instance during walking in a graded exercise program Since serious interference with the diffusion of oxygen and carbon dioxide occurs more commonly in pulmonary emphysema than in any other chronic illness, the factors responsible for impairment of respiratory function will be carefully appraised by our various contributors In this chapter the consequences of the disturbed pulmonary physiology, including especially hypoxia, are outlined as a background for the administration of oxygen and helium oxygen mixtures, certain additional aspects of the mechanism of dyspnea are described as a basis for other forms of physiologically directed therapy, such as the clinical application of pressure breathing

Both acute and chronic arterial *hypoxia occur in the majority* of cases of pulmonary emphysema, manifested by a lowered oxygen saturation of the arterial blood, or by a therapeutic response *to oxygen inhalation at rest or after* exercise In addition

to a long-standing type of oxygen-want, more severe acute hypoxia takes place at times as a result of bronchopulmonary infections and exacerbation of bronchospasm Since hypoxia, a term considered more accurate to describe a lowered tension of oxygen in the tissues than anoxia, is so characteristic of this clinical entity, the effects of abrupt deprivation of oxygen on the human individual will be appraised from the standpoint of the uncomplicated syndrome of acute hypoxia, which has been clarified through experiments on men and animals exposed either to a diminished pressure or concentration of oxygen in the inhaled atmosphere.

Pathologic Changes Resulting from Acute Hypoxia

Although it has been long recognized that the central nervous system is especially vulnerable to hypoxia, studies on the gradient of reaction in different parts of the brain have revealed that the small pyramidal cells of the cortex are far more sensitive than the medulla and spinal cord The cerebral cortex may manifest severe damage as a result of hypoxia maintained for 2 to 10 minutes, depending upon the experimental technique employed, furthermore, Morrison found that the frontal lobe cortex was more readily damaged by graded hypoxia than the rest of the brain cortex and other parts of the central nervous system The available evidence strongly supports the assumption that the more recently developed elements in the central nervous system are more sensitive to injury, possibly because they require a higher oxygen consumption for maintenance of normal function

Cerebral hypoxia can be produced not only by the production of a lowered tension of oxygen in the tissues of the body but also, as Schmidt and his colleagues have shown, by a local increase in the oxygen uptake of the brain beyond the capacity of the existing oxygen supply, as revealed by the high oxygen consumption of brain cells after administration of convulsive drugs The cerebral oxygen uptake in many instances varies directly with the degree of cerebral activity The physiologic limits of oxygen consumption

of the brain are described as being from one-half to double the resting value

The *heart* apparently is the organ next most sensitive to oxygen-want The myocardial lesions from oxygen-want are focal in distribution and found most prominently in the papillary muscle and the left ventricular wall Greater damage is experienced by older animals than young ones as a result of acute hypoxia

The effects of long continued hypoxia on the *lungs* themselves are of considerable interest As is well known, capillaries undergo an increase in permeability to serum after exposure to anoxia. When inhalation of 10 per cent oxygen was combined with inspiration under negative pressure, produced by resistance in the trachea, more pulmonary congestion and intra-alveolar edema were noted by Drinker than took place when similar pathologic states were produced by inspiratory obstruction alone (Moore and Binger, Kernan and Barach) When serum escapes from the capillaries into the alveoli at a greater rate than can be absorbed by the lymphatics or, in an unconscious subject, be removed by coughing, it accumulates within the alveoli. During periods of obstruction of the bronchioles, either partial or complete, the local hypoxia produced would therefore tend to promote localized formation of edema The application of this concept to patients with chronic obstructive pulmonary emphysema leads to an interesting speculation concerning the cause of the increased sputum which is commonly found at night and expectorated in the morning The decrease in pulmonary ventilation during sleep may result in areas of severe alveolar anoxia with a consequent increase in capillary permeability and transudation of serum into the alveoli As will be referred to again later, when patients with this disorder reside continuously in an oxygen-enriched atmosphere, a conspicuous result of treatment is the prompt decrease and, at times, disappearance of expectoration

The *adrenal gland* also is sensitive to hypoxia; animals exposed to a diminished pressure of oxygen have shown a decrease in adrenal ascorbic acid and lipid An increase in 17- and 11-ketosteroids takes place as a result of acute oxygen want in man, with a diminished tolerance for glucose and a decrease in circulating

eosinophiles. In contrast to the effect of hypoxia on oxygen-sensitive organs, the *blood supply to the extremities* may be cut off by a tourniquet for several hours without injury to the tissues of legs

Pathologic Physiology of Hypoxia

The acute disturbance in the physiology of the patient with pulmonary emphysema due to the abrupt onset of hypoxia may be understood best by noting the effects on normal human subjects of a decreased pressure of oxygen at high altitude A mistake not uncommonly made in clinical practice is to attribute the manifestations of acute oxygen want to other factors of the illness, even to bad behavior, rather than to lack of oxygen Since pathologic studies on organ sensitivity to hypoxia revealed that the brain was the most vulnerable and the heart the next most quickly affected, the disorder in the *functioning* of the human organism was correctly assumed to proceed in a similar manner During World War II extensive studies of the effect of abrupt ascent to simulated high altitude on aviators resulted in a precise formulation of the consequences of uncomplicated hypoxia Since these investigations provided information of a qualitative and quantitative nature concerning the consequences of oxygen-want of the degree found in cases of pulmonary emphysema, a brief review of some of the pertinent findings will be presented

Physical Factors Involved in the Production of Altitude Hypoxia

At 18,000 feet the atmospheric pressure is reduced from 760 mm Hg to 380 mm Hg or one-half the sea level pressure One liter of gas at this altitude would have expanded in a free state to 2 liters, the expanded volume would hold the same number of oxygen and nitrogen molecules as were present at sea level, but each molecule would be separated from every other one by a greater distance The inspired air at 18,000 feet would appear at first glance to contain one-half the number of oxygen molecules as were present in the inhaled air at sea level, but in actual fact the pressure of oxygen in the lungs is considerably less than one-half the sea level pressure because of the following consideration

Carbon dioxide and water vapor in the alveoli, both of which

are formed constantly in the lungs, occupy space that prevents inhalation of air from outside the body. In order to determine accurately the tension of oxygen in the lungs at 18,000 feet, i.e., 380 mm Hg, the following calculation is undertaken: (380 − 47) × 0.209, the percentage of oxygen in a saturated atmosphere, will give the inspired oxygen pressure. The pressure of water vapor in the lungs is 47 mm Hg, and that of carbon dioxide at sea level is 40 mm Hg. However, an individual exposed to acute hypoxia, such as would exist at 18,000 feet, would increase markedly the volume of breathing with the result that additional carbon dioxide would be blown off, and the pressure of CO_2 would be replaced by an equivalent pressure of oxygen. The acutal tension of oxygen in the alveoli might then be (380 − 47) × 0.209 minus 30 (if this was in fact the lowered carbon dioxide pressure) or 39.6 mm Hg. The respiratory quotient of 1 is assumed in these calculations.

The alveolar oxygen pressure in a normal individual at sea level is about 100 mm Hg which is sufficient to saturate the hemoglobin in the red cells to 98 per cent. At an altitude of 18,000 feet a pressure of 39.6 mm Hg of oxygen obviously will not provide the tissues with the accustomed pressure of oxygen, with the result that the function of the various organs, especially the brain and the heart, are seriously interfered with. This degree of hypoxia is equivalent to that produced by inhalation of approximately 10 per cent oxygen with 90 per cent nitrogen. As a result of the increased pulmonary ventilation and the loss of CO_2, the acid base equilibrium shifts toward the alkaline side to a considerable extent, such as a change in pH of 7.42 to 7.55, because of a relatively more rapid elimination of carbon dioxide in proportion to the adaptive reduction in the total base ions in the blood.

In Figure 2.1 the effect of decreasing barometric pressures is shown at various altitudes. The vapor pressure of water is governed by the ambient temperature and not ambient pressure. The temperature within the lung of individuals subjected to an 18,000 feet altitude remains the same as at sea level in spite of a decrease in ambient pressure of 50 per cent. Thus, the number of molecules of H_2O in any given volume remains the same at sea level as at 18,000 feet. The increased ventilatory response to hypoxia is

followed by a progressive loss of carbon dioxide which leads to varying degrees of alkalosis

The harmful effects of the hyperventilation alkalosis induced by acute hypoxia was revealed in a study of the physiologic action of 10 per cent oxygen inhalation with and without carbon dioxide in cases of coronary sclerosis and normal individuals (Barach, Steiner, Eckman and Molomut) The electrocardiographic signs of *coronary insufficiency produced by inhalation of* 10 per cent oxygen-nitrogen mixtures for 10 to 20 minutes were found to be prevented by addition of 2 per cent carbon dioxide It was interesting to note that the pH of the arterial blood was 7 46 after inhalations of the low oxygen-carbon dioxide mixtures and 7 52 after the inhalation of 10 per cent oxygen without carbon dioxide Furthermore, precordial distress did not occur when the low oxygen mixture was breathed together with carbon dioxide, but appeared when low oxygen mixtures alone were inhaled It was also observed that the depression of T wave and

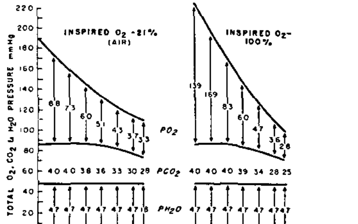

FIG 2 1 Effect of altitude hypoxia on alveolar oxygen and carbon dioxide pressure in normal subjects breathing air to 20 000 feet and 100 per cent oxygen to 40 000 feet Vapor pressure of 47 mm Hg is constant in each instance

St segment produced by *uncomplicated hypoxia was prevented* when carbon dioxide was added to a 9 per cent oxygen mixture The arterial oxygen saturation produced by this degree of hypoxia varied from 57 to 88 per cent These results appeared to indicate that the alkaline shift caused by acute hypoxia resulted in constriction of the capillary bed, additional ischemia and progressively increased hypoxia of the cardiac muscle since alkalosis itself results in oxygen being held more firmly to the hemoglobin *When the small concentration of* CO_2 *was added, the oxygen tension* in the cardiac muscle was presumably higher because of the absence of alkalosis This may have played a significant role in producing a higher T wave since it was shown that inhalation of 100 per cent oxygen itself was followed, in the majority of cases, by an increased height in the T wave

In Figure 2 2, the dissociation curves of hemoglobin reveal the characteristic lowering of the arterial oxygen pressure at a given

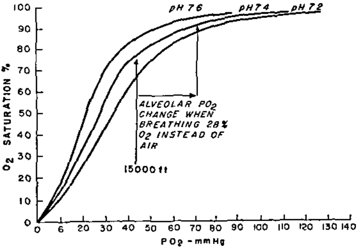

FIG 2 2 Dissociation curves of hemoglobin at normal, alkaline and acid pH. *Relatively marked increase in arterial oxygen saturation,* i e from 75 to 90 per cent, is produced by an increase from 21 to 28 per cent in inspired oxygen in the normal individual exposed to 15,000 feet, as a result of the steep slope of the curve in this area A rise of 7 per cent oxygen at this altitude is equivalent to about 3 8 per cent at sea level

oxygen saturation when the pH becomes alkaline The effe
a small increase in oxygen percentage of the inspired air, *i e*,
21 to 28 per cent, results a relatively large rise in alveolar ox
pressure when hypoxia is severe, because of the steep slo
the curve in this region, at 15,000 feet a 7 per cent increa
inspired oxygen is equivalent to approximately 3 5 per ce
sea level

Symptoms and Signs of Hypoxia

Early manifestations of disturbance in the physiology o
human organism as a result of mild oxygen want, such as
place after several hours at altitudes between 7,000 and 1
feet, are a decrease in the peripheral field of vision and dark a
tation, and increase in pulse rate A significant impairme
emotional control occurs at 12,000 feet. An increase in pulmo
ventilation at 12,000 feet results in a blowing off of ca
dioxide which is gradually compensated for by a correspon
reduction in the same bicarbonate level of the blood, a less
secretion of acid in the urine and an increase of chloride io
the blood

The arterial oxygen saturation at 10,000 feet is approxim
90 per cent, and at an altitude of 15,000 feet this is lowered
further to 78 per cent At the latter altitude, although the ox
saturation is lowered 20 per cent, the tension of oxygen in
blood may be only 41 mm Hg or less than half normal In cl
discussions concerning the factor of hypoxia in the producti
dyspnea in pulmonary emphysema, a slight lowering of
arterial oxygen saturation is at times regarded, quite erroneo
as being of little significance A decrease in tissue oxygen pre
results in a burdensome elevation of the pulmonary ventilati
these subjects, as will be seen later

After several hours exposure to altitudes of 12 000 to 1
feet, other characteristic symptoms appear, such as head
nausea and lassitude In respect to mental function, impairm
of emotional control is one of the earliest and one of the
conspicuous responses to hypoxia In some individuals over
fidence, euphoria, exaggerated self-esteem and boisterousness

outstanding manifestations of a decreased activity of the inhibitory or critical functions of the brain. This is of considerable interest since the frontal lobe cortex has been found to be damaged by hypoxia before other parts of the brain In other cases dullness, drowsiness, irritability and anger are observed. Depending upon the environment in which the effects of hypoxia are tested, impairment of emotional control may manifest itself in inability to inhibit aggressive, sexual or egoistic impulses In fact, the effects of hypoxia, as induced by decreased tension of the oxygen in the atmosphere were found by McFarland and Barach to be astonishingly similar to those resulting from alcohol, provided environmental factors were made similar in each case.

Although human subjects at an altitude of 12,000 feet generally revealed good performance in neuromuscular tests, this efficiency was shown to be strikingly impaired when remarks were made which challenged the emotional adjustment of the subject, such as irritating statements about his personality. Men who withstood criticism blandly at sea level reacted with violent hostility during exposure to moderate hypoxia in a low pressure chamber The importance of this response in civil and military aviation is difficult to overestimate but it should be recognized also that a similar state frequently exists in patients with pulmonary emphysema in whom a comparable degree of impairment of respiratory function takes place Often patients are judged adversely because of apparently immature behavior that is not characteristic of their personality during periods when they are free from hypoxia.

When lack of oxygen is severe, the pulse rate becomes more rapid, breathing is accelerated, consciousness is rapidly impaired and finally lost as a result of damage to the central nervous system, heart and other organs.

Although the brain is the organ whose function is impaired most significantly by acute hypoxia, the disturbance in function of the heart is revealed not only by the increase in pulse rate but also by a characteristic depression of the T wave of the electrocardiogram At an altitude of 15,000 feet, or during inhalation of a 12 per cent oxygen mixture, the electrocardiogram shows this characteristic change As is now well known that patients with

coronary artery disease during inhalation of 10 to 12 pe
oxygen frequently manifest not only depression of the T
but also changes in the S-T segment which confirm or est
the diagnosis of coronary insufficiency The hyperventilati
duced by hypoxia and lowered CO_2 tension plays a role in T
depression since the addition of 2 per cent CO_2 to the low c
mixture frequently prevents T wave change, as was dis
more fully above Acute coronary insufficiency may be p
tated by inhalation of 10 per cent oxygen but the sym
produced are counteracted by prompt inhalation of 100 pe
oxygen With severe hypoxia the heart is dilated, the
depending upon the severity and duration of oxygen depri

The *increase in pulse rate is a highly characteristic s*
acute hypoxia, this tachycardia represents an increased
flow when the arterial oxygen saturation is in the neighb
of 80 per cent (Asmussen and Chiodi) In studies of the circ
with the Fick technic, Cournand, Richards and their collab
observed a rise in pulmonary artery pressure as a result
halation of 10 per cent oxygen atmospheres The bearing
finding in cor pulmonale is of considerable interest, since th
ventricular systolic pressure is increased in these patie
times from 22 to 88 mm Hg

The high susceptibility of the liver and kidneys to hypo
been shown by Schorr and his collaborators, who found
vasodepressor material was elaborated by the liver in shoc
that a vasoexcitor material produced normally by the
was stopped by prolonged hypoxia such as occurs in shoc
study of the circulation in human shock by Cournand and
the cardiac output, as determined by the direct Fick techn
lowered one third in some cases with an increase in bloo
acid, a shift in pH to the acid side and a fall in oxygen satu
of the mixed venous blood from 65 to 35 per cent and in
cases, *to as low as 15 per cent In addition to the treatm*
shock by administration of intravenous fluids to overcom
discrepancy between the diminished circulating blood volu
the relatively large vascular bed, inhalation of oxygen ha
employed In experimental hemorrhagic shock in dogs the c

of oxygen in arterial, femoral vein and right heart blood has been shown to be substantially increased when 100 per cent oxygen was breathed, *i e*, 1 5 cc of oxygen per 100 cc of blood

When the onset of hypoxia is more gradual and sustained in patients with pulmonary emphysema the resultant effects are more comparable to the consequences of residence at high mountainous places, thus Heber, in discussing the symptoms of the average European at Ladak Kashmir (11,500 ft), says· "The feeling of fitness on arrival soon gives way to a terrible weariness and restlessness, especially after a short day of mental work The mental deterioration is not as serious, however, as the change in temperament and all subjective functions It is astonishing how the most decisive of men will slowly and insidiously lose the power of decision and become unwilling to bear responsibility " Barcroft noted the increase in fatigability at Cerro de Pasco (14,200 ft) and the inevitable slowness and clumsiness at all work In the clock test it took him twice as long to read the reverse face of the clock as it did at sea level He remarked that any prolonged mental effort usually involved a degree of fatigue which necessitated a trip to the coast to prevent a "nervous breakdown "

The inertia so commonly observed in patients with chronic pulmonary emphysema may well be due, at least in part, to the persistence of long-standing hypoxia, although acclimatization tends to modify the severity of reaction to some extent, as will be discussed later

Changes Induced by Relief of Hypoxia in Pulmonary Emphysema

When chronic arterial hypoxia was suddenly terminated by inhalation of 50 per cent oxygen, striking changes in mental function were observed to occur in a period of one hour to one day, in the early studies of Richards and Barach on administration of oxygen to patients with chronic heart disease, a subdued state was frequently encountered, together with a tendency for increased sleep, but an abrupt precipitation of an irrational, comatose state was observed at times in patients with chronic pulmonary emphysema In 1938 I reported that this reaction took

place in those patients who were abruptly treated with high concentrations of oxygen (*i e*, 40 to 50 per cent oxygen atmospheres) and that it could be prevented by a program of administering gradually increasing oxygen concentrations In the paper "Impairment in Emotional Control Produced by Lowering and Raising the Oxygen Pressure in the Atmosphere," I mentioned that this extraordinary psychologic change might be due to the increase of blood carbon dioxide which was produced by the diminished volume of breathing that Richards and I had demonstrated to be the characteristic consequence of inhalation of 50 per cent oxygen in cases of cardiac failure and especially chronic pulmonary emphysema When the phenomenon of increased CO_2 levels in the blood was emphasized as a cause of the comatose state by Comroe and others, I had arrived at the opinion that the increase in CO_2 tension only produced irrationality when it was accompanied by a change in pH, with a true respiratory acidosis The effects of the sudden reversal of hypoxia induced by oxygen inhalation in patients with pulmonary emphysema, especially in respect to change in mental function, were described as follows in the paper referred to above

"In those cases of pulmonary emphysema in which pre-existing arterial anoxemia has been present over a considerable period of time, the continuous administration of 50 per cent oxygen may result in a swift impairment in emotional control, proceeding to delirium in some instances This is also true of the inhalation of oxygen in patients with cerebral arteriosclerotic disease in which the brain may be assumed to suffer from pre-existing ischemic cellular anoxia In both groups of patients inhalation of high oxygen atmospheres, such as is provided by residence in a tent or oxygen room, may be followed by depression, crying spells, drowsiness, sleep, coma or delirium

"In a case of pulmonary emphysema, with moderately severe arterial anoxemia, inhalation of oxygen resulted in relief of dyspnea and cyanosis, and also in relapse into a comatose state which lasted six days At the end of this period the patient awoke *cheerful, rational and alert Before treatment he had been* apprehensive and depressed for several years, following oxygen treat-

ment he was optimistic and unworried as long as the oxygen concentration in the atmosphere was not reduced. In a woman with cerebral arteriosclerotic disease, an irrational state began within five hours after inhalation of 50 per cent oxygen. Active delirium was once observed in a man with chronic anoxia due to pulmonary emphysema after he had been in an oxygen tent for a period of one hour His arterial oxygen saturation had been 57 per cent prior to treatment

"In patients with chronic anoxia, the personality of the individual may appear normal before inhalation of oxygen, and swiftly undergo a profound change It is my impression that the first effect of breathing oxygen is a subdued state in the majority of cases I cannot, in this paper, discuss the metabolic consequences of altering the oxygen tension in these cases but it may be briefly reported that an increase in the content of carbon dioxide in the blood takes place whenever the volume of breathing is diminished by inhalation of oxygen Whether the initial depressed state is related to this effect, or to other more complex changes, cannot now be decided "

The significance of retention of CO_2 following administration of various concentrations of oxygen will be discussed later but the clinical value of the adaptation response to administration of gradually increasing oxygen concentrations has been confirmed many times since 1938 by Barach, Bickerman, Beck, Segal and, more recently, by Simpson It has become steadily more clear as a result of the studies of Schmidt, Comroe and others, that the patient with pulmonary emphysema was peculiarly dependent upon the chemoreceptors in respect to the regulation of the volume of breathing rather than arterial CO_2 tension, or pH stimulation of the respiratory center

Sensivity of the Chemoreceptors to Arterial Hypoxia

The receptors of the carotid and aortic bodies are stimulated mainly by decrease in arterial oxygen tension, which is the organisms' chief defense against hypoxia because of the resultant increase in pulmonary ventilation These chemoreceptors should be distinguished from the receptors of the carotid sinus and aortic

arch, which respond to alterations in arterial blood pressure In normal human subjects the chemoreceptors are not stimulated until the oxygen in the inspired air is lowered to 18 per cent In fact, the volume of breathing is not increased significantly until altitudes of 8,000 to 10,000 feet are obtained, corresponding to an arterial oxygen saturation of approximately 90 per cent As hypoxia is increased, however, there is a progressive rise in pulmonary ventilation as a result of stimulation of these chemoreceptors with a consequent decrease in blood carbon dioxide tension and a shift in the acid base equilibrium to the alkaline side More severe lack of oxygen impairs the function of the medullary center of the brain, produces respiratory depression and an acidosis due to carbon dioxide retention and failure of adequate oxidation of the products of metabolism

Although only a slight increase in breathing occurs in the normal subject at an arterial oxygen concentration of 90 per cent, the view that hypoxia of this degree does not play a significant role in the dyspnea of congestive failure (Harrison et al) and pulmonary emphysema (Baldwin et al) is at variance with the response of these patients to oxygen inhalation, hypoxia in congestive failure and pulmonary emphysema has been shown to be of crucial importance in maintaining dyspnea, even in cases in which the arterial oxygen saturation is lowered to this slight extent, *i e*, to between 90 and 93 per cent (Barach and Richards) The fallacy of using the response of the chemoreceptors to hypoxia in normal individuals to explain the dyspnea of patients is revealed by the marked difference in the behavior of patients and normal subjects to inhalation of oxygen

The normal individual responds to inhalation of 100 per cent oxygen with a transient increase of pulmonary ventilation of 5 to 7 per cent However, patients with congestive failure and pulmonary emphysema, in whom an arterial oxygen saturation of 90 to 93 per cent has been found, generally respond to inhalation of oxygen with a decrease in minute volume of respiration of 10 to 30 per cent Furthermore, continued inhalation of oxygen-enriched atmospheres results in progressive relief of dyspnea despite the previous presence of a normal or nearly normal arterial oxygen

saturation The sensitivity of the chemoreceptors in patients with clinical dyspnea evidently is decidedly different from that of normal human beings An undue emphasis is at times given to proprioceptive reflexes from the bronchi and lungs, which admittedly play an important role but by no means as exclusive a one as has been stated by the advocates of the reflex cause of dyspnea, since hypoxia can be demonstrated to be a most significant factor in these cases, *i e*, those whose ventilation is decreased by oxygen inhalation In addition, the arterial oxygen saturations may be found to be normal at times due simply to the effect of the hyperventilation that so often accompanies the drawing of arterial blood in patients, which results in a fictitiously higher saturation than would be present under actual basal conditions

Patients with pulmonary emphysema have been studied repeatedly in our clinic who maintain a burdensome degree of pulmonary ventilation with the result that the arterial blood is almost normally saturated with oxygen Similarly, patients with congestive failure, in addition to a stagnant hypoxia due to a decreased cardiac output, frequently manifest only a slight lowering of the arterial oxygen saturation In both groups the dyspnea is often relieved markedly after one or two days of breathing 50 per cent oxygen, even at a time when the degree of pulmonary congestion is not decreased, as demonstrated by no increase in the vital capacity Since the reduction in pulmonary ventilation as a result of a test inhalation of 100 per cent oxygen frequently is between 15 and 30 per cent, the hypoxic factor evidently is of considerable importance in the maintenance of dyspnea and it cannot be minimized, therefore, by a report of a normal or nearly normal arterial oxygen saturation Unless it has been shown that oxygen inhalation, comfortably and properly administered, is ineffective in reducing the volume of breathing, the chemoreceptors must be acknowledged to play a more significant role in the dyspnea of pulmonary emphysema than in the respiration of normal people The increment in pulmonary ventilation due to the effect of hypoxia on these bodies constitutes a large proportion of the maximal breathing capacity of these patients, a circumstance that also ministers to the subjective sensation of dyspnea

Hypoxia Caused by Depression of the Respiratory Center

When an individual has received an overdose of a barbituric acid derivative or other respiratory depressant drugs, the pulmonary ventilation is reduced below normal, and the pressure of oxygen in the arterial blood falls The respiratory center is depressed, as demonstrated by the failure of these cells to respond to increased concentrations of carbon dioxide Under these circumstances, reflexes from the chemoreceptors are of manifest importance, since breathing is then stimulated by hypoxia at a time when the respiratory center is depressed by the narcotic The regulation of respiratory function has changed from the delicate one of carbon dioxide and its resultant effect on pH to the more primitive type produced by lack of oxygen Under these conditions inhalation of 5 to 10 per cent carbon dioxide does not increase significantly the volume of breathing and is not indicated, since a high CO_2 tension in the blood and respiratory acidosis already are present Inhalation of 100 per cent oxygen is followed by a sharp fall in respiratory activity and is, therefore, contraindicated, but arterial hypoxia nevertheless must be treated by oxygen in moderate concentrations, adequate to relieve anoxia If a decrease in pulmonary ventilation takes place of a degree that causes respiratory acidosis, additional means of ventilating the patient should be provided i e, by mechanical methods, such as intermittent pressure breathing devices, the tank respirator or the exsufflator as well as medications which do stimulate respiration such as benzedrine and caffeine Intravenous injection of sodium lactate may be employed also to combat respiratory acidosis In pulmonary emphysema a decrease in pulmonary ventilation of harmful proportions does not generally take place as a result of the properly regulated program of administration of oxygen unless sedative drugs have been used in addition Even if respiratory depression and acidosis are present, oxygen treatment should not be abandoned but rather continued, with an effective form of artificial respiration as long as is necessary since damage to brain cells must be prevented if at all possible and since the provision of a normal arterial oxygen tension is itself helpful in restoring the

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Patients with pulmonary emphysema have been studied repeatedly in our clinic who maintain a burdensome degree of pulmonary ventilation with the result that the arterial blood is almost normally saturated with oxygen Similarly, patients with congestive failure, in addition to a stagnant hypoxia due to a decreased cardiac output, frequently manifest only a slight lowering of the arterial oxygen saturation In both groups the dyspnea is often relieved markedly after one or two days of breathing 50 per cent oxygen, even at a time when the degree of pulmonary congestion is not decreased, as demonstrated by no increase in the vital capacity Since the reduction in pulmonary ventilation as a result of a test inhalation of 100 per cent oxygen frequently is between 15 and 30 per cent, the hypoxic factor evidently is of considerable importance in the maintenance of dyspnea and it cannot be minimized, therefore, by a report of a normal or nearly normal arterial oxygen saturation Unless it has been shown that oxygen inhalation, comfortably and properly administered, is ineffective in reducing the volume of breathing, the chemoreceptors must be acknowledged to play a more significant role in the dyspnea of pulmonary emphysema than in the respiration of normal people. The increment in pulmonary ventilation due to the effect of hypoxia on these bodies constitutes a large proportion of the maximal breathing capacity of these patients, a circumstance that also ministers to the subjective sensation of dyspnea.

Hypoxia Caused by Depression of the Respiratory Center

When an individual has received an overdose of a barbituric acid derivative or other respiratory depressant drugs, the pulmonary ventilation is reduced below normal, and the pressure of oxygen in the arterial blood falls The respiratory center is depressed, as demonstrated by the failure of these cells to respond to increased concentrations of carbon dioxide Under these circumstances, reflexes from the chemoreceptors are of manifest importance, since breathing is then stimulated by hypoxia at a time when the respiratory center is depressed by the narcotic The regulation of respiratory function has changed from the delicate one of carbon dioxide and its resultant effect on pH to the more primitive type produced by lack of oxygen Under these conditions inhalation of 5 to 10 per cent carbon dioxide does not increase significantly the volume of breathing and is not indicated, since a high CO_2 tension in the blood and respiratory acidosis already are present Inhalation of 100 per cent oxygen is followed by a sharp fall in respiratory activity and is, therefore, contraindicated, but arterial hypoxia nevertheless must be treated by oxygen in moderate concentrations, adequate to relieve anoxia If a decrease in pulmonary ventilation takes place of a degree that causes respiratory acidosis, additional means of ventilating the patient should be provided, i e , by mechanical methods, such as intermittent pressure breathing devices, the tank respirator or the exsufflator, as well as medications which do stimulate respiration, such as benzedrine and caffeine Intravenous injection of sodium lactate may be employed also to combat respiratory acidosis In pulmonary emphysema a decrease in pulmonary ventilation of harmful proportions does not generally take place as a result of the properly regulated program of administration of oxygen unless sedative drugs have been used in addition Even if respiratory depression and acidosis are present, oxygen treatment should not be abandoned but rather continued, with an effective form of artificial respiration as long as is necessary, since damage to brain cells must be prevented, if at all possible, and since the provision of a normal arterial oxygen tension is itself helpful in restoring the

sensitiveness of the respiratory center to carbon dioxide. In
spiratory paralysis due to poliomyelitis, with or without the ef
of sedation, an adequate ventilation of the respirator will prev
a CO_2 acidosis, even though supplementary oxygen adminis
tion is required

Hypoxia in the Presence of a Normal Tension of Oxygen in the Arterial Blood

When tissue hypoxia is present in patients in whom the arte
oxygen saturation is normal, the chemoreceptors of the caro
and aortic bodies are not stimulated, and the pulmonary venti
tion is not increased In cases of carbon monoxide poisoning,
which oxygen-want is produced because of the greater affinity
hemoglobin for CO than for O_2, the arterial oxygen saturation
the remaining hemoglobin is normal The pulmonary ventilati
is not elevated, although an increase in cardiac output of appro
mately 25 per cent has been found with a 50 per cent carbon mo
oxide hemoglobin concentration The blood pressure is not rai
significantly by hypoxia, but the pulse rate is elevated

Similarly, in moderately severe anemia the pulmonary venti
tion is not significantly elevated since the arterial oxygen satu
tion is normal, but Richards and Strauss found the cardiac outp
elevated In patients with pulmonary emphysema, inhalation
cigarette smoke has the possibility of aggravating dyspnea b
cause of accumulation of carbon monoxide in the blood, in
normal individuals Barach, Eckman and Molomut found a
average arterial CO concentration of 5.7 per cent after inhali
smoke of 20 cigarettes McFarland has found even more serio
hypoxic effects from the increased carbon monoxide in the bloo
than we have

In patients with congestive heart failure the oxygen pressu
in the tissues may be reduced substantially as a result of a sta
nant type of hypoxia, but a slight lowering of the arterial oxyge
saturation generally is also present as described above

Another variety of tissue hypoxia in the presence of a norma
arterial oxygen saturation is that caused by drugs which exer
an adverse effect upon cellular respiratory enzymes, so-calle

venous oxygen saturation of from 20 to 33 per cent and an elevation of the partial pressure of oxygen from 14 to 21 mm Hg

The relief of severe coronary insufficiency in cases of coronary thrombosis treated by oxygen is a good illustration of the importance of increase in physically dissolved oxygen (Levy and Barach) That angina pectoris was a syndrome caused by hypoxia of the myocardium was pointed out by Keefer and Resnick but Boland pointed out that pain in coronary thrombosis and severe angina pectoris was more apt to be relieved by inhalation of 100 per cent than 50 per cent oxygen Observations of the author indicate that inhalation of 100 per cent oxygen for periods of 20 minutes three times daily results in a reduction in the number and severity of attacks of anginal pain in patients who have many seizures daily Furthermore, in obliterative arterial disease of the extremities continuous inhalation of 50 per cent oxygen has been found to relieve pain and to promote healing of gangrenous ulcers *Because of valvular arteritis in rheumatic fever ischemia of the* heart valves has been held responsible for valvular disease itself; inhalation of oxygen during the acute disease was believed responsible for a low incidence of valvular heart disease in patients treated by *Poulton Taran has stated that, although oxygen* therapy does not reduce measurably the duration of rheumatic activity, cardiac disability is minimized significantly The use of oxygen in the treatment of cerebral thrombosis was suggested by *Poulton, who found in a small series of cases that the end results* in oxygen-treated cases appeared to indicate less brain damage than might have been expected The evidence recited above is strongly suggestive of the value of oxygen treatment of ischemic hypoxia under the circumstances described The application of these findings to the pathophysiologic disturbance found in the patient with pulmonary emphysema has been mentioned previously and will indeed become clarified in subsequent chapters

Methods of Increasing Resistance to Hypoxia

During the war, methods of increasing resistance to hypoxia were studied, primarily because of interest in high altitude aviation Lowering of the total oxygen consumption by thyroidectomy

was found to result in a marked increase in tolerance to hypoxia in experimental animals. This approach, made use of by Blumgart in the treatment of cardiac insufficiency, was tried in cases of pulmonary emphysema. Relief of dyspnea was obtained in some patients; if myxedema is prevented by administration of thyroid extract, the procedure appears to be justified in selected cases.

Of the drugs employed to increase the resistance of the organism to hypoxia, ammonium chloride is a good example of a physiologic alteration of the individual that resulted in a gain in altitude tolerance, *i.e.*, between 2,000 and 2,500 feet. A metabolic acidosis, produced by ingestion of 30 gm. of enteric-coated ammonium chloride over a period of two days, resulted in an increased ventilation without the hazard of alkalosis with a fall in alveolar and arterial pCO_2 of approximately 6.5 mm. Hg. At an altitude of 42,000 feet, during an inhalation of 100 per cent oxygen, administration of ammonium chloride produced a net rise in arterial oxygen saturation from 78.7 to 84.8 per cent and in arterial oxygen tension from 41.9 to 53.1 mm. Hg (Barach and associates). The increased pressure of oxygen available to the tissues was due to the more acid blood, which permitted the unloading of oxygen to the cells with a greater head of pressure at a given arterial oxygen saturation, as well as the higher arterial oxygen tension itself. The use of ammonium chloride has not been subjected to special study in cases of pulmonary emphysema but like Diamox, which also produces an acidosis that results in a lowering of the blood CO_2 tension, may be beneficial in some cases due, in our opinion, primarily to its diuretic effect. Both drugs are hazardous as a treatment for acute severe respiratory acidosis since they add a metabolic acidosis.

In a patient with far advanced pulmonary fibrosis who had been kept alive for seven months by residence in an oxygen room at 50 per cent oxygen, a comatose state developed suddenly when she was taken out of the chamber and given nasal oxygen. Ammonium chloride was given, 18 gm. in eighteen hours on the day before death with the thought of displacing the retained blood carbon dioxide. The arterial CO_2 content fell from 132 to 128 and finally to 120 volumes per cent five hours before death. The arterial

CO_2 tension was then calculated approximately at 120 mm. Hg. (data from Richards and Barach) It would appear that ammonium chloride administration added the harmful effects of a metabolic acidosis I have since then reported the beneficial effects of intravenous injection of sodium lactate following which the pH promptly rose and the comatose state markedly lessened, with clinical recovery subsequently

In Figure 2 3 the metabolic consequences of ammonium chloride are seen to be a rise in arterial oxygen pressure as consequence of the substitution of oxygen for the displaced CO_2 Under conditions of altitude hypoxia in normal individuals, the benefit from such respiratory stimulation was clearly evident. Furthermore, no impairment of mental function was discerned from the metabolic acidosis produced In patients with pulmonary emphysema, however, ammonium chloride has been of value as a preparation for administration of mercurial diuretics, but whether any valuable purpose would be accomplished by using it as a method of diminishing CO_2 retention is highly questionable, as will be made more clear in the discussion on Diamox

Attempts to decrease acute hypoxia at high altitude by conscious hyperventilation did not prove to be of value in our experience even though the arterial oxygen pressure often can be markedly increased by overbreathing at altitudes of 13,000 to 20,000 feet, but the parallel decrease in arterial carbon dioxide tension seemed to Eckman and me responsible for failure of improvement in mental functioning. However, Otis, Fenn and their

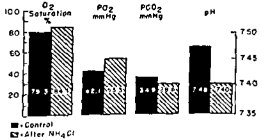

FIG 2 3 Rise in arterial pO_2 and fall in pCO_2 following ingestion of ammonium chloride in healthy subjects produced by ventilatory stimulus of a metabolic acidosis

collaborators presented good physiologic evidence in support of their belief that optimal tensions of oxygen and carbon dioxide could be produced for various altitudes. The deliberate employment of hyperventilation is, however, of no clinical value to the average conscious patient with pulmonary emphysema for reasons that will be discussed later and it is not possible of achievement in the presence of respiratory acidosis and semi-comatose states.

The inhalation of carbon dioxide does diminish hypoxia at moderate altitudes because the increased pulmonary ventilation raised the alveolar oxygen percentage but it was more practical as well as more comfortable to inhale oxygen-enriched atmospheres. Carbon dioxide therapy has no value to the patient with pulmonary emphysema, even for the production of cough and expectoration, since diffusion of CO_2 is manifestly impaired in these cases. In addition, the abnormally small ventilatory response to CO_2 inhalation characteristic of these cases is not reversible (Fishman, Samet and Cournand).

The effect of diet on resistance to hypoxia at altitude has been studied over a long period of time. A high carbohydrate diet results in an increased R.Q., a higher production of carbon dioxide with a given oxygen consumption produces a proportionate rise in alveolar ventilation and, therefore, in arterial oxygen tension. At high altitudes, where 100 per cent oxygen is breathed, differences in the metabolic R.Q. would not affect the alveolar R.Q. which always remains at unity, and, therefore, no benefit could be expected under these circumstances. At altitudes such as at 15,000 feet, where air is breathed, the comparison between results of a high carbohydrate meal and a high fat-protein meal showed that an increase in ceiling altitude of 1,000 to 2,000 feet took place. However, in cases of pulmonary emphysema an increased CO_2 production does not result in an increased volume of breathing, and diet plays no special role in this entity.

Decrease of Altitude Hypoxia by Breathing Oxygen under Positive Pressure

The inhalation of oxygen under continuous positive pressure by a mask was introduced clinically in 1935 for the treatment of left-sided heart failure by Poulton in England and for the treat-

ment of acute pulmonary edema and obstructive dyspnea in this country by Barach and his associates Pressures between 4 and 13 cm of water were used therapeutically for these disturbances in respiratory function The reason for employing pressure breathing at high altitudes was to increase the arterial oxygen pressure and thereby effect a gain in altitude tolerance (Gagge and Allen). Since the purpose of pressure breathing was to increase the efficiency of performance at any specified high altitude, the degree of pressure that could be tolerated and the effects of these pressures were studied extensively during the war When oxygen was breathed under an added pressure applied continuously throughout the respiratory cycle, it was called *continuous positive pressure breathing* (C P P B) Intermittent positive pressure breathing (I P P B) is the procedure in which the mask pressure is *considerably higher at inspiration that at expiration. The effect* of the added ventilatory pressure on the circulation, venous pressure rise and cardiac output was found to be equivalent to the mean increase in pulmonary pressure. The alveolar oxygen pressure was additionally elevated by the induced hyperventilation

When oxygen is inhaled by a mask under continuous positive pressure, the added mask pressure results in an increase in arterial oxygen pressure equal to that which would have been obtained if the barometric pressure itself had been raised correspondingly. If the breathing pattern is unchanged, and the alveolar CO_2 is constant with pressure breathing, then the added mask pressure is added to the alveolar oxygen pressure If air were inhaled, then the increase in alveolar oxygen pressure would be only ⅕ of the added mask pressure since air contains 20 9 per cent oxygen This procedure was therefore of value at altitudes higher than 34,000 feet, at which the inhalation of 100 per cent oxygen compensated for this degree of altitude anoxia At an altitude of 42,4000 feet the arterial oxygen tension, when subjects breathed pure oxygen at 15 mm Hg mas pressure, was found to be the same as that present at an altitude of 40,000 feet breathing pure oxygen without pressure. A gain of 2,400 feet in altitude was thus produced by this procedure, this accomplished an increase of

from 80 to 89 per cent in arterial oxygen saturation (Gagge, Barach, Fenn, Hemholz and others)

The use of a pressure as high as 15 mm Hg, however, was attended by a decreased cardiac output in the majority of normal individuals of the order of 20 to 25 per cent lower than control values as determined by both the ballistocardiograph and the Fick method The vertical diameter of the heart was increased The electrocardiogram showed characteristic changes due to the rotation of the heart with notably a depression of the T wave In normal individuals about 40 to 50 per cent of pressure applied at the mask was found to be absorbed by the elasticity of the pulmonary parenchyma and the bronchi, the remainder being passed on to the intrapleural space and the outside of the heart The venous pressure was elevated approximately 40 to 50 per cent, which maintained a return of blood to the right side of the heart at a high level of intra-auricular pressure The systolic blood pressure rose almost as much as the applied mask pressure so long as the cardiac output remained constant

With intermittent pressure breathing the highest pressure was during inspiration and the lowest pressure varied from zero to one-third the inspiratory pressure The increase in the arterial oxygen pressure was achieved in part by the mean average pressure and in part from the hyperventilation induced by intermittent pressure breathing, since some alveolar CO_2 was replaced by oxygen However, the gain in arterial oxygen pressure as a result of a loss of CO_2 did not in our own studies represent an increase in efficiency of the subject because excessive hyperventilation produced alkalosis and, at times, tetany Even in the absence of tetany the performance of individuals tested with intermittent pressure breathing did not always correspond to the gain in arterial oxygen pressure achieved by a loss in carbon dioxide Furthermore, in respect to the increase in altitude attained by pressure breathing, continuous P B was more comfortable than an equivalent mean pressure derived from intermittent pressure breathing, although the modern devices for I P P B have been found effective for the treatment of pulmonary edema and respiratory acidosis

Although an individual with a tendency to underventilate would be benefited by a certain degree of hyperventilation, a valuable exchange of more acapnea for less anoxia was difficult to achieve, especially when consideration is given to the significant diminution in cerebral blood flow that accompanies passive hyperventilation of moderate degree. Although theoretical evidence, as mentioned above, supports the use of moderate hyperventilation to overcome altitude hypoxia (Fenn, Otis et al.), its use at barometric pressures near sea level, either voluntarily or by mechanical means, is fraught with the hazards of the hyperventilation syndrome both in normals and dyspneic subjects.

Hyperventilation of moderate intensity was found by Schmidt and his associates to be accompanied by a decrease in cerebral blood flow of 30 per cent with a reduction of cardiac output of approximately 11 per cent It is of interest in this connection to point out that about 20 per cent of the total cardiac output and 24 per cent of the total oxygen consumption are devoted to the brain, which is only 2 per cent of the body weight The effect of marked hyperventilation at sea level is to decrease approximately 40 per cent the arterial oxygen pressure, to which the brain cells are exposed Carryer has stressed the importance of the respiratory alkalosis produced by hyperventilation, manifested clinically by anxiety, giddiness and confusion A reduction of the carbon dioxide in the serum from 45 to 15 mm Hg brought about an alkalotic state which, according to his calculations, reduced by 61 per cent the amount of oxygen released in the tissues The symptoms and signs of hypoxia may also be produced in the emphysematous patient with normal pH by immoderate routine hyperventilation

The Acclimatization Response to Prolonged Hypoxia

The acclimatization response to high altitudes, such as 22,000 feet, has been recently studied by Houston and Riley through the use of low pressure chambers in which men were exposed to a gradual decrease in barometric pressure produced over a period of 30 days. Although there was an average 37 per cent increase in hemoglobin, as measured by the oxygen capacity, an additional

major compensatory response appeared to be an increased pulmonary ventilation, which to a degree increased the arterial oxygen pressure, lowered the pCO_2 and, secondarily, the blood bicarbonate Although the arterial pH shifted to the alkaline side, the production of an injurious alkalosis was prevented by the buffering action initiated by loss of bicarbonate through the kidneys The oxygen consumption of the subjects did not change and, although the tissues were exposed to a considerable degree of hypoxia and cellular function presumably impaired, the subjects themselves felt well and considered themselves in good condition With an increase in cardiac output the decreased AV difference raised the venous pO_2, thereby increasing the mean capillary pO_2 and aiding the delivery of oxygen to the tissues A marked reduction in pO_2 gradient occurred between arterial and mean capillary blood, a reduction due primarily to the inherent characteristics of hemoglobin

A study* of the response of a patient with advanced metastatic cancer to similar gradually decreasing oxygen concentrations revealed interesting comparative data The patient was acclimatized to 10 per cent oxygen, equivalent to an altitude of approximately 18,000 feet, during a period of 35 days Although the oxygen saturation and tension of arterial blood fell to a level comparable to the average values of the subjects studied by Houston and Riley at a comparable altitude, the pH of the blood shifted to the acid side rather than toward alkalinity This metabolic acidosis appeared to be the result of severe impairment of the function of the liver, due to the presence of large metastases, as well as, presumably, the effect of hypoxia on an already damaged organ The patient was not short of breath during the period of residence in the low oxygen atmosphere, except when walking The volume of the pulse, which was markedly diminished during the last two days at an oxygen concentration of 10 per cent, improved on return of the patient to atmospheric pressure It was noteworthy that the red count was unchanged at 3 9 million although in

* Barach, A L, Holaday, D, Graff, S, Beck, G, and Bickerman, H A Physiologic effect of acclimatization to hypoxia in a patient with advanced metastatic cancer To be published

normals tested at similar degrees of hypoxia a rise in red blood corpuscles from 4 5 to about 7 millions, depending on the length of exposure to altitude, takes place

In reviewing the respiratory features of acclimatization to altitude Riley, Otis and Houston point out that the low oxygen pressure and the high pH found during exposure to altitudes between 18,000 and 22,000 feet have deleterious effects upon cellular function, that the ventilatory changes are such as to suggest that a balance is struck between the evils of hypoxia and hypocapnia and that acclimatization to altitude is a matter of adjustment to a low pCO_2 as well as to a low pO_2 During the period of adaptation the whole blood buffer base is reduced by selective excretion of fixed base and retention of fixed acid by the kidneys This process, in the terminology of Singer and Hastings, leads to metabolic acidosis which is secondary to the respiratory alkalosis The pH of the blood which may be elevated to the vicinity of 7 6 is restored toward normal as a result of continued base excretion provided the acclimatization process is successfully carried out for a sufficient time As a result of the loss of base a further increase of ventilation and lowering of pCO_2 becomes possible without excessive elevation of pH An important consequence of the increase in ventilation and lowering of pCO_2 is naturally the accompanying elevation of alveolar pO_2

However, when the subject returns quickly to sea level, his ventilation continues at the high rate and returns to normal very gradually over a period of days or perhaps weeks The explanation of this appears to be the acid base mechanism which stimulates ventilation sufficiently to prevent the pH of arterial blood from falling much below 7 40 Because the acclimatized subject has at this time a low buffer concentration in the blood, the arterial pCO_2 must be kept correspondingly low to prevent respiratory acidosis, *i e*, by maintenance of a high pulmonary ventilation When the buffer base is increased the ventilation decreases If these considerations are kept in mind in reference to mechanical hyperventilation of the emphysematous patient, it will be seen that continued loss of pCO_2 must be followed by a loss in buffer base with the result that the patient has the burden of eliminating

carbon dioxide produced in the body by a degree of augmented ventilation that may indeed result in dyspnea, because of the restricted nature of the pulmonary bellows. Unless the diffusion capacity of his lungs had been notably improved by other measures acidosis would appear to be more likely to take place on activities resulting in increased CO_2 production.

Although Fishman, Samet and Cournand believe that elimination of carbon dioxide as accomplished by Diamox therapy may restore mental alertness and a sense of well-being and diminish the threat of CO_2 narcosis, our opinion is that this sequence of events is not apt to take place in patients who have developed the homeostatic mechanism of eliminating CO_2 at a higher pCO_2 tension without acidosis. It is true that the metabolic acidosis produced in healthy subjects by ammonium chloride did not result in the irrationality that is initiated when a CO_2 acidosis takes place. However, in the many patients whom we have observed, oxygen treatment was followed by a gradual rise in arterial CO_2 content to a range between 80 and 100 volumes per cent with a maintenance of normal pH and an alert mental state. The increased CO_2 concentration in the alveolar air, which results in a greater elimination of carbon dioxide per unit of ventilation, is not a completely successful mechanism but it does appear to permit the decreased breathing engineered by the effect of oxygen on the carotid sinus to take place without the development of an undue fall in pH and with relief of shortness of breath, as will be discussed again in the section on oxygen therapy. This adaptive mechanism, which is illustrated schematically in Figure 2-4, in which it will be seen that the same quantity of CO_2 may be eliminated with a decreased tidal air if the expired CO_2 is proportionately elevated.

A slight increase in the requirements for gas exchange in the lung which results in a moderate increase in pulmonary ventilation may nevertheless initiate severe dyspnea in patients that have mechanical difficulty in breathing. The work of breathing which is *to some extent dependent on the volume of breathing* is lessened by inhalation of oxygen both at rest and during exercise. The mechanism of adaptation of the patient with pulmonary

between periods of rapid respiration due to the increased washing out of carbon dioxide with 80 per cent helium and 20 per cent oxygen as contrasted to the record obtained with a patient breathing air The period of apnea breathing air was 2 0 seconds, when breathing the helium oxygen mixture 12.4 seconds. The sensation of air hunger was notably diminished Other tracings revealed the effect of helium on the mechanics of breathing in bronchial asthma and pulmonary emphysema, with and without added intrapulmonary pressure (1934–1938)

In a study by Eckman and me, a motor was employed to raise and lower a weight to a spirometer bell at a constant number of revolutions per minute The inlet of the spirometer was constricted to between 0 31 and 0 75 inches. Comparisons were made between the extent of filling of the spirometer bell and the pressure within the system, when the apparatus breathed helium oxygen mixtures instead of air the tidal air increased 23 to 50 per cent, with decreased pressures between 2 and 21 per cent. When oxygen alone was employed there the contrast was even more evident due to increased molecular weight of oxygen. A brief experiment with hydrogen gave slightly better results than with helium

Maytum, commenting on the good results obtained in four cases of intractable asthma with the clinical use of the helium oxygen mixture, reported by Prickman, Boothby and himself, observed subsequently concerning inhalation of helium with oxygen. "I consider it to be the most valuable treatment at present for status asthmaticus and to be of definite value in the treatment of other obstructive lesions of the respiratory tract . It is of the greatest value in cases of transient obstruction and if the lesion is in the larynx, tracheotomy may be avoided in some cases This is particularly true in cases of postoperative or traumatic edema of the larynx and of transient paralysis of the cord occasionally seen after thyroidectomy "

Eversole studied the use of helium-oxygen mixture in cases of partial obstruction of the larynx or trachea and reported that of 105 cases 55 obtained complete relief, 37 partial relief and 13 no relief from inhalation of helium-oxygen therapy. The number of studies confirming the value of inhalation of helium with oxygen

when properly administered in patients with intractable asthma and obstructive dyspnea, including those of Segal, Kernan, Bickerman, Beck and others, have made it clear that the physical work of breathing was diminished and that diffusion of gases in the helium atmosphere was increased

In pulmonary emphysema bronchial constriction is less localized, however, as a consequence of its higher diffusion capacity inhalations of helium and oxygen may penetrate alveoli that may be relatively impermeable to air or oxygen Furthermore, an advantage necessarily takes place when obstruction to flow is due to turbulent resistance which, as shown elsewhere in this book, is increased in cases of pulmonary emphysema with an augmented ventilation A sensation of relief is generally noticed by these patients during inhalation of 80 per cent helium and 20 per cent oxygen Since hypoxia is so frequently present in this disease, 25 to 30 per cent oxygen with the remainder helium has been employed at times for 15 to 20 minutes three times daily The administration of these mixtures is generally carried out with the Meter mask in order to avoid rebreathing of carbon dioxide, often with the expiratory pressure attachment set 4 cm H_2O Mixtures of 25 to 30 per cent oxygen and 75 to 70 per cent helium are also employed in intermittent pressure and continuous breathing devices to accomplish more efficient aeration of the alveoli and to reduce the respiratory effort The routine administration of helium-oxygen mixtures in cases of bronchial asthma and pulmonary emphysema has declined in recent years The increasing use of corticosteroids, especially prednisone, combined with continuous nebulization of bronchodilator aerosols, have rendered the problem of bronchospasm more amenable to treatment There are, nevertheless, instances of severe dyspnea in which combinations of helium with oxygen combined with pressure breathing serve a useful purpose, the decreased ventilation that often follows the use of these procedures is associated with a more efficient diffusion of oxygen and carbon dioxide In Figure 2 5, the effect of inhalation of 20 per cent oxygen and 80 per cent helium under a continuous pressure of 4 cm H_2O is seen to produce a decrease in the volume of breathing from 8,560 to 6,940 cc per minute

accompanied by a diminution in the length of the expiratory cycle This patient appeared to have a type of obstructive dyspnea associated with bronchitis obliterans, in addition to pulmonary emphysema and fibrosis

Oxygen Therapy in Pulmonary Emphysema

Inhalation of oxygen is instituted in many cases of pulmonary emphysema when an acute exacerbation of the disease takes place, manifested by severe dyspnea, cyanosis, tachycardia and,

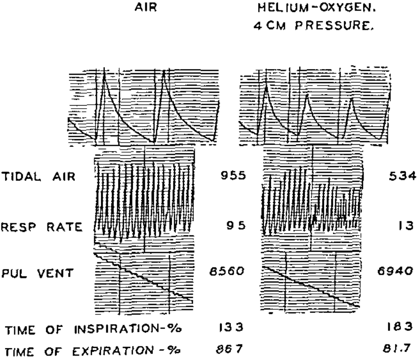

Fig 25 Spirometric records in a patient with pulmonary emphysema, pulmonary fibrosis and chronic bronchitis reveal the unusually long duration of expiration spontaneously adopted by the patient The diminution of dyspnea ... with 20 per cent oxygen under ... decrease in pulmonary ... tidal air from 955 to 534 ... prolonged expiration

(Barach, A L, Am J Surg, 89: 376, 1955)

at times, mental confusion Arterial hypoxia and CO_2 retention are increased and, in some cases, accompanied by an acid shift in pH Abrupt impairment of respiratory function takes place most commonly as a result of infection, either viral in nature due to the common cold or atypical pneumonitis, or as a result of pyogenic bronchopulmonary disease Other pathophysiologic events that result in a worsening of the emphysematous state include intractable bronchospasm as a result of exposure to allergic agents or refractoriness to bronchodilator drugs, alveolar overdistention following undue severe physical exercise, and failure of the right or left heart

The determination of the peripheral venous pressure is naturally helpful in estimating the degree of insufficiency of the right ventricle, along with other evidences of cor pulmonale, as will be discussed by Richards and Fishman (Chapter 15) Failure of the left ventricle is far more difficult to detect since the breath sounds are diminished and moist rales are infrequently audible In either event, the administration of oxygen is a specific measure for rapid correction of the circulatory disturbance induced by hypoxia, it is also more effective than other forms of cardiac therapy, as shown by Dexter and associates, who reported that the cardiac output was restored toward the normal when it was elevated, as in cases of pulmonary emphysema and cor pulmonale with increase in total pulmonary resistance and also when it was lowered, as a result of the added load of poor oxygenation on an already overworked heart muscle

The indication for treatment is the continuous, not intermittent, inhalation of oxygen in such a manner as to relieve hypoxia without the development of unfavorable reactions Abrupt exposure to an atmosphere of 40 to 50 per cent oxygen is rarely necessary to save life since substantial relief of oxygen want may be provided by the inhalation of 25 to 30 per cent oxygen The most practical method of obtaining the objective of a graded increase in oxygen concentration consists in the use of the rubber catheter inserted in the nasal pharynx or, if desired, into the oropharynx This should be removed regularly at six-hour intervals and greased with K-Y jelly After several days, when the patient is in better

control of his physical and mental faculties, a double bent nasal catheter or plastic tube, which is inserted one-half inch within the nares, is substituted since it is far more comfortable and provides an adequate concentration of oxygen in the inspired air with suitable flows

The program of oxygen administration, originally outlined in 1938, consists of a flow of 1 or 2 liters per minute for the first 24 hours, with an increase of 1 liter per minute every day or, in the event of increasing drowsiness, every other day until a flow of 7 liters per minute is attained This will generally result in a concentration of approximately 38 per cent in the inspired air, varying somewhat with the degree of hyperventilation. At this time, if desired, an oxygen tent may be substituted with a concentration of 40 per cent oxygen, maintained with a flow of 10 to 12 liters per minute and sufficient leakage to insure that the atmosphere does not contain more than 40 per cent oxygen by test If cardiorespiratory compensation appears to be substantially restored at the end of one to two weeks' additional treatment the double nasal tubes are reinserted with an oxygen flow of 7 liters per minute, a gradual decrease in the administration of oxygen takes place by lowering the flow one liter per minute every other day or every other day until the patient is returned to an air atmosphere This method is to be preferred to the employment of oxygen intermittently. The latter procedure is fraught with the hazard of sudden changes of oxygen tension which leads to the patient becoming addicted to oxygen The consequence of employing intermittent oxygen therapy is not simply the abrupt precipitation of dyspnea when a mask or a tent is removed as the effect on mental function, manifested in most cases by the patient feeling dizzy, restless and anxious, long before shortness of breath takes place With the method of gradually decreasing the oxygen concentration, compensations develop, including an increase in hemoglobin and red blood count, elevated pulmonary ventilation and decrease in blood bicarbonate

This program is not apt to be followed by respiratory acidosis and coma if sedatives are withheld Morphine is lethal and the barbiturate undesirable Paraldehyde is preferred by Simpson

who, having observed the comatose state as a result of
ministration of high concentrations of oxygen, recently
". . I have, more recently, used this method in severely
disoriented patients and have avoided coma, which, I fe
would have supervened had they been put at once into an
tent I therefore now use Barach's method in every case
those in which urgency demands the use of an oxygen tent
in the tent is by no means necessarily fatal Even if the
dies in the tent, it must be remembered that the severity
infection, the duration and degree of the anoxia, and the
status all have important bearing on the immediate pr
. Except when a patient's critical situation demands
oxygen is now given initially by nasal catheter and the fl
is gradually increased to avoid coma Respirators have
little use with comatose patients since the rhythm of t
pressed but functioning respiratory center cannot be pa
by the machine "

The measures employed in the treatment of respiratory a
discussed in this volume by Chermack (Chapter 14),
applicable to the prevention of the syndrome In ou
Demerol in small dosages, 25 to 40 mg at 6-hr intervals
ferred as a sedative since in this dosage unaccompanied b
sedatives, it does not depress the respiration and functio
bronchodilator as well If mental confusion or somnolen
during the program outlined above, caffeine sodium ben
employed, 0 5 to 1 0 gram at 4- to 8-hr intervals, or ca
used at 8-hr intervals with Benzedrine, 20 mg intramu
during the alternate 4 hr period as effective drugs for stin
an increased ventilation The mechanical methods of aug
the volume of breathing may also be used as additional
the prevention of respiratory acidosis It is, to our mind, a
mistake in judgment to withdraw oxygen, or to give it i
tently, in these cases, since the respiratory center is furth
aged by hypoxia as well as the function of the heart and th

Since an increase in the CO_2 tension of the arterial b
evitably follows oxygen therapy if the pulmonary ven
and, consequently, the dyspnea, is decreased this rete

CO_2 is not necessarily alarming unless the pH of the blood is changed toward the acid side A small shift in pH as a result of CO_2 retention may be followed by mental changes if it takes place rapidly The comatose state is not, therefore, called carbon dioxide narcosis in our clinic but respiratory acidosis. Frequently, a very considerable degree of carbon dioxide retention is found prior to oxygen treatment as a result of impaired diffusion plus the administration of sedatives It is not commonly recognized that the *arterial blood Co_2 may be lowered as a result of oxygen treatment* Following the initial rise, for example, from an arterial CO_2 content of 65 to 85 or 90 volumes per cent during a three week period of oxygen treatment, the carbon dioxide may gradually fall to 70 volumes per cent and then later, during inhalation of air, to 60 volumes per cent This reduction in blood CO_2 is not produced artificially by mechanical hyperventilation but takes place as a result of improvement of the function of the lungs and therefore better diffusion of CO_2

The fall in blood carbon dioxide during oxygen therapy seems to me to offer crucial evidence in this respect. In Figure 2 6 and and Figure 2 7, data from the studies by Richards and me reveal the decrease in arterial CO_2 content in a patient with pulmonary fibrosis and cardiac insufficiency respectively. It will be seen that the initial rise in carbon dioxide, accompanying the relief of dyspnea and decrease in ventilation, was followed by a decrease in CO_2 during continuation of oxygen therapy as the vital capacity of the lungs increased, in the patient with cardiac failure, the compensatory elimination of chlorides, precipitated by the early rise in carbon dioxide, played a role in the diuresis that is often characteristic response of oxygen therapy, especially marked in cases with pulmonary emphysema and right or left heart failure The pCO_2 in this case fell from 40 to 36 mm Hg *during oxygen treatment*, with the pH not significantly altered, or slightly elevated.

The clinical results of oxygen treatment in emphysema include a progressive diminution in the volume of breathing, a prompt lowering of the pulse rate, with a diuresis in cases of cardiac insufficiency, a decrease in alveolar distention, and a remarkable

diminution in expectoration Whether this is due to a cessation of the hypoxic influence on capillary permeability or to a diminution in the previously existent locally applied excessive negative pressures during inspiration or to some other cause, the fact itself is an indication that bronchial constriction has been alleviated Physiologically based measures that aid diffusion of oxygen and carbon dioxide, which in themselves improve the bronchopulmonary function, are preferable to mechanical ventilation, these

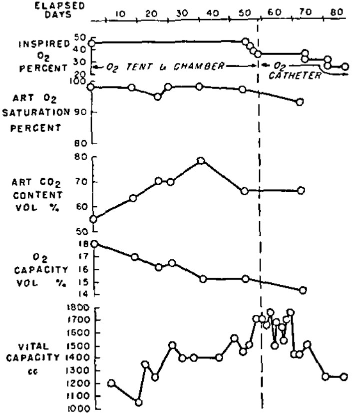

FIG 2 6 Decrease in arterial CO_2 content, following an initial rise, produced during oxygen therapy in a patient with pulmonary fibrosis Improvement in respiratory function revealed by rise in vital capacity

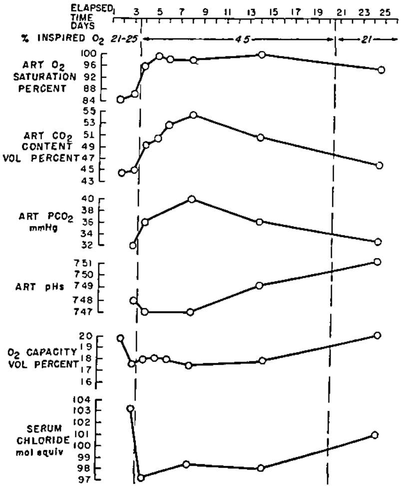

FIG. 27 Decrease in arterial pCO_2 following an initial rise in a patient with cardiac insufficiency during continuous oxygen therapy, with compensatory fall in chlorides (Data from Richards, D W., Jr, and Barach, A L, Quart J Med, 24: 437, 1954)

measures include the use of prednasone, antibiotic therapy, bronchodilator aerosols, and medication by drugs during the period of oxygen treatment

It has been emphasized that the presence of high CO_2 concentrations in the blood has created undue alarm since it has not been

understood by some writers on this subject that a high alveolar CO_2 also allows the patient to take advantage of the lower pulmonary ventilation engineered by inhalation of oxygen because the higher partial pressure of CO_2 facilitates diffusion of the gas into the alveoli The expired carbon dioxide is not as high as it might be because of inadequate ventilation of some of the alveoli, especially in bullous areas of the lung, but the homeostatic nature of the retention of CO_2, although initially caused by organic disease, is of sufficient importance to warrant additional discussion Arbitrary efforts to lower the elevated blood CO_2 in the absence of a true respiratory acidosis, manifested by pH change, have the disadvantage of destroying this mechanism The patient then, on exercise, may rapidly develop increased CO_2 retention with acid shift in pH because the buffer bicarbonate reserve was previously lowered by a hyperventilation program In my opinion, the employment of hyperventilation devices is not indicated, except in cases with a true respiratory acidosis This view is not, however, held by some of the advocates of I P P B Thus, Fishman, Samet and Cournand have not apparently been impressed by the adaptive changes described by Richards and me over a period of many years nor by a similar point of view expressed by Christie and Riley but appear to believe that "the action of increased CO_2 tension is a depressant of physiologic and mental processes, which occasionally progresses to the stage of narcosis and death "

These authors further state that the compensatory elevation of CO_2 would result in a lowering of the arterial pO_2 while breathing CO_2-free air However, in the large number of cases with a normal or nearly normal arterial oxygen saturation the effect of the drop in pressure due to increased pCO_2 is small indeed, because of the relatively flat shape of the dissection curve of hemo globin in this range The calculation of the effect produced is made on the basis of the formula referred to in the discussion of altitude hypoxia Thus $760 - 47$ (water vapor) $= 713$, the inspired air pressure 713×21 (oxygen per cent in the atmosphere) $= 150$, the inspired oxygen pressure Deducting 40 mm Hg for the alveolar pCO would give 110 mm Hg, if the alveolar

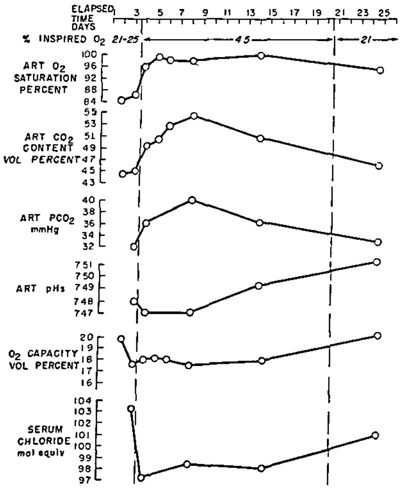

FIG 2 7 Decrease in arterial pCO_2 following an initial rise in a patient with cardiac insufficiency during continuous oxygen therapy, with compensatory fall in chlorides (Data from Richards, D W., Jr., and Barach, A L, Quart J Med, **24:** 437, 1954)

measures include the use of prednasone, antibiotic therapy, bronchodilator aerosols, and medication by drugs during the period of oxygen treatment

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pCO_2 was elevated to 50, the alveolar oxygen pressure would be *100 mm Hg, which would have an insignificant effect in these* cases of pulmonary emphysema. In instances in which the alveolar pCO_2 rises to 60 to 80 mm Hg during oxygen therapy, the alveolar pO_2 is raised by the increased concentration of the inhaled atmosphere and, therefore, offsets the dilution factor of an increased tension of carbon dioxide In severe hypoxia the steep slope of the dissociation curve accounts for the fact that administration of even low concentrations of oxygen, *i e.*, 28 per cent, results in a relatively large increase in arterial oxygen concentration (*cf.* Fig 2) The adaptive chemical changes in the arterial blood were indeed originally reported in hypoxic patients who were tested by oxygen therapy. In summary, granted that a rise in pCO_2 of from 40 to 60 mm will decrease the pO_2 from 110 to 90, assuming an R Q of 1, this 20 mm. fall in O_2 could be fully compensated (under normal conditions) by an increase of 3 per cent in the oxygen concentration of the inspired air A 1 per cent increase at sea level is equivalent to a 7 13 change in inspired pO_2. Naturally, in pulmonary emphysema the increase in inspired oxygen would be somewhat higher to produce a similar increase in oxygen absorbed into the arterial blood

Comroe has, in fact, recently confirmed our finding of an adaptive mechanism in a case history reported in a panel discussion by Cullen and associates, as follows:

"Patients with pulmonary disease who develop CO_2 retention over a long period of time seem to get along pretty well. Dr. Francis Wood has a patient at the University Hospital who was kept alive for a year or two by the use of nasal oxygen. We measured his arterial pCO_2 at different times during that period of 2 years, it increased from 60 mm of mercury to 85, and then to 140 mm. of mercury and stayed there for a year or more. During all this time he was alert, jolly and even quite witty, so he certainly was not narcotized

"Therefore, over long periods of time, there must be some compensation so that people can tolerate very high tensions without any gross damage."

It is of considerable interest that the cerebral blood flow was

found to be markedly elevated as a result of inhalation of oxyge and the accompanying rise in arterial CO_2 tension in 6 of 9 case reported by Patterson, Heyman and Duke Sudden changes n oxygen tension, both above and below that to which the individ ual is accustomed, may in themselves play a role in alteration in mental function in addition to the effect of a respiratory acido sis or alkalosis In a case of hypoventilation associated with en cephalitis reported in 1921 by Barach and Woodwell, inhalatio of 80 per cent oxygen for $1\frac{1}{2}$ hours produced a rise in arterial CO content from 64 to 88 volumes per cent as the arterial oxyge saturation rose from 60 to 84 per cent Had mechanical hyper ventilation procedures been employed at that time to prevent CO_2 acidosis, the cerebral blood flow would presumably not hav been elevated, at any rate the indication for prevention of abrup carbon dioxide retention is now clear in any case in which dimin ished volume of respiration is present

The secondary increased excretion of chlorides as a result c elevation of CO_2 after oxygen therapy was also shown to play role in the initiation of a diuresis in cases of cardiorespirator failure This response seemed to be in part responsible for restora tion of compensation in some cases of congestive heart failur that were refractory to other measures

In the accompanying x-ray illustration (Fig 2 8), the respons of a man of 66 with pulmonary emphysema and clinical evidenc of right and left heart insufficiency is shown before and after oxy gen therapy and biweekly injections of mercuhydrin The inte lobar effusion cleared and the size of the heart decreased on th combined therapy, dyspnea was relieved within several hour after inhalation of approximately 40 per cent oxygen was begui even though previously resistant to bed-rest and digitalis, Ir creased rest and sleepiness were clinically evident as effects c the therapeutic program which ultimately resulted in restoratio of circulatory compensation Irrationality was not provoked b oxygen therapy but drowsiness was present for four days, in a probability the consequence of CO_2 retention, and a slight c moderate fall in pH, although no measurements of the arteri blood gases were made

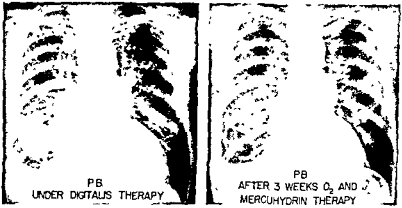

FIG 2 8 Following three weeks of continuous inhalation of 40 per cent oxygen and biweekly injections of mercuhydrin the heart size was markedly diminished and the fluid in the pleural space between the right middle and lower lobes cleared

It should be emphasized that oxygen therapy in itself is not dangerous. The danger lies in an unwarranted curtailment of oxygen therapy. In these cases of severe hypoxia a small increase in alveolar oxygen results in a relatively large increase in arterial oxygen saturation, because of the steep slope of oxygen dissociation curve During the last twenty years confused mental states, have been encountered at times but infrequently when the program of gradual increase and gradual lowering of the oxygen concentration delivered to the patient has been followed, with the precautions mentioned above. If indeed stupor does take place when low oxygen concentrations are employed, sedatives should be withheld or counteracted by drugs which stimulate the ventilation, the indication is certainly to continue treatment.

The oxygen tent is the most comfortable method of administering oxygen as well as a hygienic atmosphere produced by the air conditioning units now available. If the injector of the Meter mask is employed through a separate opening into the tent canopy, low concentrations of oxygen may be given without accumulation of carbon dioxide and with small oxygen flows. Thus, at a meter setting of 40 per cent, one liter of oxygen passing through the meter into the tent draws with it 3 14 liters of air. If the gauge

is set at 6 liters per minute the total air-oxygen mixture entering the tent is 25 liters per minute. The actual oxygen concentration in the tent at this setting is in practice between 30 and 33 per cent because of additional leakage under the canopy, the CO_2 in the tent atmosphere is below 1 per cent There are meters available with a larger orifice in the injector which provides 32 per cent oxygen At an oxygen flow of 4 liters the air-oxygen mixture passing through the meter into the tent is 28 liters per minute, *i e*, 6 liters of air to 1 of oxygen. Because of leakage the tent atmosphere is less, 25 to 27 per cent. Since the air-conditioned tent is more comfortable than the nasal catheter, it can be used with the method outlined above It should be realized that the replacement of the air atmosphere with an air-oxygen mixture must have sufficient volume to dilute the carbon dioxide concentration below 1 per cent In Leonard Hill's bed-tent oxygen was blown across the subject's face for this purpose but no provision was made to keep the tent atmosphere itself hygienic in terms of the heat, moisture or carbon dioxide given off by the patient. In our early development of the ventilated oxygen tent, calcium chloride and soda lime were used but later cooling coils were substituted for cooling and dehumidification The suggestion of Rosenbleuth and Block to dispense with soda lime by increased oxygen flows was adopted but it must be understood that a patient with fever may have a CO_2 production of 300 cc per minute which would require an entrance into the tent, either by leakage or an injector, of 30 liters per minute The claim made at times that a tent, hood or face tent will provide 50 per cent oxygen at a flow of 6 to 8 liters per minute without undue accumulation of carbon dioxide cannot be substantiated Thus, 8 liters of O_2 plus 22 liters of air will dilute the CO_2 to 1 per cent in cases with a CO_2 production of 300 cc per minute, but the oxygen concentration of the com-

himself if necessary when the nurse is not present, such as when he needs to go to the bathroom in a hurry The inside zipper often provides a feeling of mental security in that the patient has less

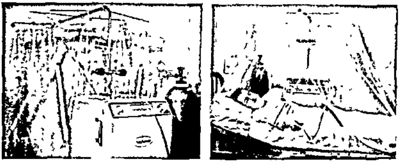

Fig 2 9 The photograph illustrates the inside zipper opening which permits the patient to release himself when indicated and also the attachment with two injector meters, by which either 33 to 40 per cent oxygen or 45 to 70 per cent oxygen can be administered At the 33 per cent meter setting, 6 liters per minute of oxygen result in a total flow into the tent of 42 liters of 32 per cent oxygen; at a 40 per cent meter setting 10 liters per minute of oxygen result in a total flow of 41 liters of 40 per cent oxygen The actual concentration of oxygen in the tent is generally 5 per cent below the meter setting.

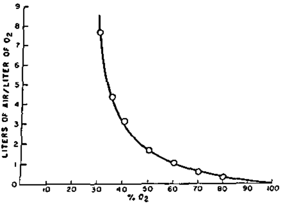

Fig 2 10 The chart illustrates the increased quantity of air drawn into the injector at low meter oxygen settings Thus, to obtain a total flow above 30 liters per minute, 5 liters per minute of oxygen would draw 30 liters of air, or a total

the mask

of the sensation of claustrophobia; if anything dire should happen he would be able to leave the tent by himself through the large opening provided The tent with the meter attached and the new canopy is illustrated in Figure 2 9

The injector meter is also used in connection with the administration of oxygen with the closed head tent The latter device, used mainly for nebulizing watery or detergent aerosols, is not so comfortable as either the air-conditioned cabinet with the enlarged canopy that covers the entire bed or the more recently introduced small portable oxygen tent

In Figure 2 10, the volume of air delivered into a tent, hood or a mask at different oxygen settings of the injector is presented It will be seen, for example, that 1 liter of oxygen will draw in twice as much air at 32 per cent as at 40 per cent oxygen

Oxygen Inhalation during Walking Exercise

In 1951, two patients with pulmonary emphysema were reported by Barach, Bickerman and Beck in whom dyspnea on exertion was markedly relieved during inhalation of oxygen, this response served as a basis for instituting an exercise program that resulted in a marked improvement in pulmonary reserve in some of these cases, as manifested by subsequent increased capacity for moderate exertion breathing air The method employed consisted of the inhalation of 8 to 10 liters per minute of oxygen through the double plastic nasal tubes, by which approximately 40 to 43 per cent oxygen is provided in the inspired air, while the patient strode back and forth across the room The substantial improvement that takes place at times seems to be due to an increase in circulatory efficiency as well as in general physical fitness The emphasis placed by Rappaport, Mayer and other writers referred to in Chapter 1, on lack of physical training as a cause of shortness of breath appears to be well borne out by the favorable responses of these patients to exercise during inhalation of oxygen

Although the program is modified to the individual case, walking 50 to 100 steps, with the nasal tube in place at an oxygen flow of 10 liters, is generally feasible, with the addition of 100 steps

daily until the patient takes 500 to 1,000 steps two or three times each day The patient is *encouraged to take half the number of* steps breathing air each day unless undue dyspnea develops. When a progressive improvement in ability to walk with lessened dyspnea takes place, after a period of a month or two, it has been presumed that a physiologic response, similar to the effect of the training program in athletes, has been produced It has been apparent that the *rise in pulse rate after walking is considerably less* following an adequate period of exercise with oxygen than at the onset of treatment although no correlation could be found with the measurement of the vital capacity.

In a study of 240 patients with chronic diffuse obstructive emphysema by Miller, Fowler and Helmholtz, the arterial oxygen *saturation was found to be normal in half of this group, even* after exercise Twenty-three per cent had hypoxemia at rest and the additional 27 per cent developed hypoxemia during a standard exercise test. Although the incidence of hypoxemia was reported to be greater in patients with more marked clinical disability, the presence or absence of hypoxemia did not govern the degree of disability in individual cases. *Cor pulmonale with congestive* failure when present occurred almost exclusively in patients who had either transient or persistent hypoxemia. These findings are of considerable interest especially in view of our observation that the majority of patients with pulmonary emphysema reveal a significant reduction in pulmonary ventilation during the inhalation of 100 per cent oxygen, whether the arterial oxygen saturation is lowered, nearly normal or normal.

Our conclusion has been that these cases maintain an augmented volume of breathing, even though it is burdensome, with the result that the arterial oxygen saturation is thereby restored toward the normal level and, furthermore, that inhalation of oxygen is manifestly a highly significant factor in the reduction of dyspnea Our data tends to support the view that in cases in which the pulmonary ventilation is immediately reduced by inhalation of 100 per cent oxygen benefit will be derived from the oxygen exercise program outlined above. There are, unquestionably, instances in which the relief of dyspnea achieved by

inhalation of oxygen is inadequate to support exercise, especially in advanced cases and those with pulmonary fibrosis as well However, a considerable number of patients, encouraged to overcome the inertia so frequently present in this entity, have recorded both subjective and objective improvement It is of interest to report that in two cases in which the program was abandoned for three months a return to dyspnea on slight exertion was manifested, in each instance subsequent utilization of the oxygen exercise program was followed by increased well being and increased capacity for exertion

Quantitative tests of cardiac and pulmonary function are not available to support the clinical impression described above, except for the observation that the pulse rate, even after a short period of two or three weeks' exercise during inhalation of oxygen, does not rise as high as was observed during the control tests Among the difficulties of interpreting pulmonary function tests and their alteration by a long term program is the fact that a steady state can rarely be achieved, since ups and downs in the patient's condition spontaneously take place and numerous other therapies are so frequently altered during the period of observation Nevertheless, it seems reasonable to state the following (1) exercise increases the cardiopulmonary reserve of normal individuals exposed to suitable training programs, (2) lack of physical fitness is characteristic of middle-aged and older people, (3) patients with pulmonary emphysema are especially prone to loss of physical fitness because of their tendency to dyspnea on slight exertion, (4) many patients with pulmonary emphysema are enabled to perform a walking exercise during inhalation of 8 to 10 liters per minute of oxygen in relative comfort and without shortness of breath, and (5) the continued use of an oxygen exercise program in some of these cases is followed by evidence of improved cardiopulmonary reserve, as manifested by less dyspnea and a decrease in tachycardia on exertion

The technique of making this type of exercise possible has consisted in the use of a 50-ft length of rubber tubing attached to a high pressure oxygen cylinder and regulator A small portable three-wheel truck has also been used which contains a G cylinder

holding 320 liters of oxygen and a handle by which the patient can push the truck up and down the hospital corridor. A small oxygen regulator is used to which is attached a 4-ft length of rubber tubing to connect with a double bent nasal catheter or plastic nasal tube A still smaller regulator has been used with the G cylinder or with a 5-lb carry-around oxygen bottle containing 160 liters of oxygen suspended from the shoulder. A modification of this cylinder is being studied, which may be more conveniently carried on the back

At a flow of 8 liters per minute the large oxygen cylinder commonly in use would provide more than 12 hours of walking exercise The smaller cylinders may be easily used in the hospital, by an oxygen therapy company, or if desired, by the patient himself with the use of three large cylinders connected with a manifold For patients who carry out this program at home, the large oxygen cylinder with the 50-ft length of rubber tubing is the least expensive The double bent plastic tubes or nasal catheters are more comfortable than any other form of oxygen therapy for this purpose, however, if higher concentrations are desired to accomplish more relief of dyspnea a setting of 50 to 60 per cent with the Meter mask, especially with expiratory positive pressure of 2 to 4 cm H_2O, may be used with an oxygen flow of 15 liters per minute

Masks are employed to administer oxygen intermittently, concentrations between 50 to 100 per cent, for the treatment of severe hypoxia, for aerosolization of bronchodilator aerosols with the nebulizer attached to it, and for the joint use of oxygen and aerosols with expiratory pressure breathing The Meter mask has several important advantages over the B L B Carbon dioxide in the collecting rubber bag is kept below 0.2 per cent even at low oxygen flows by means of an inspiratory valve Oxygen concentrations of 45 to 100 per cent may be accurately administered by the setting on the injector The mask can be operated to provide concentrations of oxygen between 33 and 40 per cent at low oxygen flows, *i e*, 4 to 6 liters per minute, with minimal resistance and without building up of CO_2 The carbon dioxide in the rebreathing bag of the B L B apparatus at these rates of oxygen

delivery varies between 1.5 to 2.5 per cent, which manifestly is undesirable in patients with emphysema. The intermittent inhalation of oxygen by mask for periods of 15 minutes three or four times a day has been used to relieve dyspnea, reduce pulmonary distention or overcome the so-called oxygen debt that may be present in hypoxic cases, a concentration between 40 and 60 per cent is generally adequate.

Clinical Application of Pressure Breathing

The clinical use of continuous pressure breathing was introduced in 1935 to aid the mechanics of breathing primarily through its effect on the respiratory passageway and on the circulation. No significant increase in arterial oxygen tension would be expected as a result of the physical effect of the increased pressure since the alveolar oxygen PO_2 would be elevated less than 1 per cent at sea level with the use of 5 to 7 mm. Hg mean mask pressure in contrast to the gain mentioned earlier of 2,500 feet when 15 mm. Hg was used to overcome hypoxia at a 40,000 feet altitude.

The immediate reaction to breathing through a constricted orifice is an increase in the intrapleural negative pressure during inspiration and a decreased negativity in an intrapleural pressure in expiration. In animals subjected to prolonged experimental tracheal obstruction, the inspiratory intrapleural negative pressure increases progressively, with the end result that marked congestion at the bases of the lungs produces severe hypoxia. The inhalation of oxygen then results in a decrease in the volume of breathing and a corresponding drop in intrapleural negative inspiratory pressure. When a mixture of 80 per cent helium and 20 per cent oxygen is inhaled during the early phase of the experiment the intrapleural negative pressure during the inspiratory cycle is decreased because of the physical laws governing effusion or turbulent flow. If air is breathed at this time under a continuous positive pressure of 5 to 6 cm. H_2O, an almost proportionate reduction in the inspiratory negative pressure in the intrapleural cavity was found and, as a consequence of inspiratory flow being physically facilitated, a consistent decrease in the volume of breathing took place. We also observed in one of our patients

with severe status asthmaticus that the inspiratory intrapleural negative pressure was reduced 4 cm H_2O by continuous pressure respiration with an 80 per cent helium and 20 per cent oxygen mixture.

The effort of breathing during the inspiratory cycle is relieved by pressure breathing primarily because of this decrease in the negative pressure required for inflation of the lungs. The maintenance of a positive pressure during expiration involves the added use of the abdominal and intercostal muscles to expel the inhaled air which has no adverse effect on the respiratory system but, as shown by Barach and Swenson, had the physiologic advantage of increasing the diameter of the smaller bronchi in patients with bronchial asthma and thereby decreasing obstructive dyspnea. Other studies have since revealed that increased lung volume and bronchial dilatation are characteristic consequences of pressure breathing An additional advantage of pressure breathing, suggested by Comroe, is that the lengthening of the bronchial tree may decrease distorted curving of the bronchioles

Pressure breathing was also employed clinically as a measure of critical value in acute pulmonary edema due to left ventricular failure or to changes in permeability in the pulmonary epithelium occurring in pneumonia and gas poisoning. Effective control of edema has been produced with expiratory pressure, continuous and inspiratory intermittent pressure breathing The mechanism through which improvement takes place includes the factors discussed above but in the main the benefit is linked to the increased pooling of blood in the peripheral vascular system, manifested, as revealed in the studies of Barach, Martin and Eckman, by a characteristic rise in venous pressure, thus, in normal individuals about 40 per cent of the applied intrapulmonary pressure was found by these authors to be counterbalanced by a comparable rise in arm venous pressure, in pulmonary congestion due to cardiac insufficiency the venous pressure rose considerably higher, 60 per cent or more, depending on the degree to which the lungs and chest wall absorbed the remainder of the applied pressure. The pulmonary capillaries in our opinion were presumably constricted by the increased pulmonary pressure, decreasing the

dency for serum to escape into the alveoli The effect of pres-
e breathing varies with the degree of pressure applied and the
te of the circulation but it tends to retard the inlet of blood
o the right auricle and thereby enables the heart to pump
re effectively with a smaller volume, an advantage in cases of
monary emphysema with left heart failure, as well as in cases
"cardiac asthma" (paroxysmal passive pulmonary congestion)
l pulmonary edema

Intermittent positive pressure breathing, originally employed
resuscitation and later, during World War II, to overcome
itude hypoxia, was used by Motley, Gordon, Theodos and
iers in conjunction with continuous nebulization of broncho-
ator aerosols in the treatment of patients with pulmonary
physema The value of intermittent pressure breathing itself
pends primarily on the principles described above in the appli-
ion of continuous positive pressure breathing, in addition, the
P B devices in current use increase the pulmonary ventila-
n, which is beneficial when indicated for the treatment of
piratory acidosis

Intermittent positive pressure breathing employed as an ad-
ict to the continuous nebulization of aerosols of the broncho-
ator type will be discussed by Fowler, Miller and Helmholz
d by Bickerman However, a critical re-evaluation of the prin
oles involved in its therapeutic application is also pertinent to
is discussion A statement is commonly made to the effect that
e rapid fall in expiratory pressure with I P P B produces a
gh velocity expiratory gas flow which promotes bronchial
ainage In comparative studies on exsufflation, which will be
esented by Beck, no physical effect on the movement of bron-
ial secretions was evident with the relatively slow expiratory
lume flow rates achieved with the use of I P P B apparatus
order to move mucus, either clinically, in experimental studies
dogs or in artificial lung apparatus, the velocity of air flow
ust be in the neighborhood of that produced by the human
ugh to produce a demonstrable physical effect The fact that
e patient frequently expectorates bronchial secretions after a
eatment appears to be due to the dilatation of the bronchi

accomplished by epinephrine and the consequent freeing of the mucus from the bronchial wall since I.P.P.B. when employed without nebulizing drugs does not produce this effect

The statement that I P.P.B. may cause cardiac embarrassment or should not be used in cardiac failure also requires clarifying comment Motley, Cournand, Werko, Dresdale, Himmelstein and Richards, in studies on intermittent positive pressure breathing, showed that cardiac output was less impaired when the expiratory pressure curve showed a rapid rather than a gradual fall. This result may be explained, at least in large part if not entirely, by considering the slope of the pressure curve as a function of the mean applied pulmonary pressure, as indicated by earlier studies reviewed by Barach, Fenn, Schmidt and Ferris, and more recent investigations of Maloney, Whittenburger and associates, Beck and Barach, on the effect of various types of pressure on the venous return The effect of the mean pressure depends not only on its degree but manifestly also on the state of the circulation. In peripheral circulatory failure entrance of blood into the right heart is already handicapped and a substantial increase in intrapulmonary pressure may be followed by more severe cardiac failure On the other hand, in cases of cardiac insufficiency, the decrease of blood entering into the heart may itself result in an increased cardiac output, i e, 10 to 35 per cent (Cournand, Werko) This response appeared to be due to a decrease in filling pressure of the right auricle, permitting the ventricle to empty more completely, and correlates well with McMichael's study of cardiac output in heart failure in which the application of tourniquets to the extremities diminished the venous return and increased the cardiac output, in accordance with Starling's law of the heart However, in right heart failure, cardiac insufficiency may be aggravated by I P P B as indicated by the studies of Miller, Fowler and Helmholz reported in this volume.

In reviewing the literature published between 1936 and 1950, Bickerman and Beck collected 64 cases in which positive pressure breathing had been employed for pulmonary edema or obstructive dyspnea Of these, 28 were in pulmonary edema due to acute left ventricular failure; 14 suffered from status asthmaticus or ob-

structive dyspnea, 13 had pulmonary edema secondary to respiratory depression, 6 were patients with an extensive pneumonic process, 1 had lung edema due to chlorine gas inhalation and 2 cases followed tracheotomy These authors reported 3 additional patients in which the application of continuous pressure breathing was followed by disappearance of lung edema It is, therefore, precisely because of the increased mean positive pressure supplied by I P P B or any other form of supra-atmospheric pressure breathing, provided an optimal pressure is employed, that the function of the failing heart may be improved, as has been observed clinically

An undue elevation in intrapulmonary pressure has produced the syndrome of peripheral circulatory failure, at high altitudes, where a mean pressure of 15 mm Hg was employed, the subjects at times collapsed after a needle was put into the artery for purposes of testing the oxygen saturation The pain, presumably associated with a fall in peripheral venous pressure, aggravated the damming-back effect of the high intrapulmonary pressures, and the arterial blood pressure then fell The method proposed in 1938 of determining whether or not the degree of positive pressure administered was excessive consisted of determining whether the arterial blood pressure fell unduly during treatment, an injurious degree of continuous (or mean) pressure was suspected when the arterial blood pressure decreased 15 mm Hg or more Although this test may not be the only or the best method of estimating the presence of an unfavorable effect on the circulation, it has appeared to be in our experience a feasible and reliable guide Other simple measurements of the physiologic effect of pressure breathing in an individual patient included the rise in venous pressure above the control value, which revealed the degree of pressure passed on to the peripheral circulation, since a small rise occurred in subjects with normal lungs and a marked increase in cases with congestive failure, in which the elasticity of the lungs was impaired and, therefore, did not expand and absorb more of the applied pressure If the chest and abdomen were completely restricted from an increase in volume by a pressure vest, the venous pressure rise was then 100 per cent of the

accomplished by epinephrine and the consequent freeing of the mucus from the bronchial wall since I P P.B when employed without nebulizing drugs does not produce this effect.

The statement that I P P B. may cause cardiac embarrassment or should not be used in cardiac failure also requires clarifying comment Motley, Cournand, Werko, Dresdale, Himmelstein and Richards, in studies on intermittent positive pressure breathing, showed that cardiac output was less impaired when the expiratory pressure curve *showed a rapid rather than a gradual fall. This* result may be explained, at least in large part if not entirely, by considering the slope of the pressure curve as a function of the mean applied pulmonary pressure, as indicated by earlier studies reviewed by Barach, Fenn, Schmidt and Ferris, and more recent investigations of Maloney, Whittenburger and associates, Beck and Barach, on the effect of various types of pressure on the venous return The effect of the mean pressure depends not only *on its degree but manifestly also on the state of the circulation.* In peripheral circulatory failure entrance of blood into the right heart is already handicapped and a substantial increase in intrapulmonary pressure may be followed by more severe cardiac failure On the other hand, in cases of cardiac insufficiency, the decrease of blood entering into the heart may itself result in an increased cardiac output, *i e*, 10 to 35 per cent. (Cournand, Werko) This response appeared to be due to a decrease *in filling pressure of the right auricle, permitting the ventricle to empty* more completely, and correlates well with McMichael's study of cardiac output in heart failure in which the application of tourniquets to the extremities diminished the venous return and increased the cardiac output, in accordance with Starling's law of the heart However, in right heart failure, cardiac insufficiency may be aggravated by I P P B as indicated by the studies of Miller, Fowler and Helmholz reported in this volume.

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applied intrapulmonary pressure, *i.e.*, all the applied pressure was transmitted to the peripheral venous system.

The circulation time was also employed as a simple method of determining the effect of pressure breathing since it was only slightly prolonged with a mean pressure of 6 cm. H_2O in normal individuals and markedly prolonged, *i.e.*, 50 to 100 per cent in patients with cardiac insufficiency Bickerman and Beck found that the cardiac impact was reduced as a result of continuous pressure breathing at 6 cm H_2O, as estimated by the ballistocardiograph, the reduction in calculated "cardiac output" was, in most instances, proportional to the mean applied pressure

Other alterations that have been recorded as a result of pressure breathing include a rotation of the heart, with an increased vertical diameter of the chest, a consequent depression of the T-wave of the electrocardiogram, an increase in hematocrit and total proteins as a result of hemo-concentration

The relation of the volume of the lung to the applied intrapulmonary pressure was studied by Fenn and his collaborators, and others who will be referred to in Chapters 9 and 11 on the studies on compliance In respect to the clinical application of inspiratory pressure, a significant factor that warrants consideration is the duration of the inspiratory pressure in augmenting lung and tidal volume Thus, in our studies with the exsufflator a peak positive pressure of 20 mm Hg with a 2 5 second inspiration produced the same tidal volume as a peak pressure of 40 mm Hg achieved in 1.6 seconds Since the hazard of tearing of an emphysematous bleb is directly related to the increase in lung volume rather than the pressure itself, it became evident that the duration of pressure should not be so sufficiently prolonged as to result in undue pulmonary distention With the use of exsufflation with negative pressure an abrupt termination of inspiratory pressure, from plus 20 to 40 mm. Hg peak pressure to a 40 mm. Hg negative pressure in 0 02 seconds resulted in a mean mask pressure actually lower than that commonly found with a 15 mm Hg inspiratory pressure, either as employed in a tank respirator or in intermittent pressure breathing devices. Graphic records on a Statham Strain Gauge of the character of mask pressure curves

s I P P.B apparatus with E W N P revealed that the y phase consumed one second or more in I P P B, ap-n contrast to a duration of positive expiratory pressure conds with E W N P With the employment of negative in expiration the mean pressure can be maintained at eric level or below the atmosphere depending upon the the negative pressure cycle

nportance of employing a negative pressure phase in al respirators to maintain a low mean pressure and prevent peripheral circulatory failure was emphasized ney, Whittenburger and associates Birnbaum and n reported some years ago that inspiratory lung inflating followed by expiratory negative pressures have favorable the circulation of deeply anesthetized dogs that were ved by supra atmospheric intermittent pressure breath of interest to note that mouth to mouth insufflation, an form of inspiratory intermittent pressure breathing, was loyed as a medical procedure by Tossach in 1743 How-ical records provide an even earlier example of successful on of this kind of pressure as a therapeutic agent, Elisha he son of a Shunnamite woman who had apparently d for some time by putting his lips over those of the nd breathing his spirit into the lungs of his spiritual

noted during World War II that the application of con pressure breathing to overcome altitude hypoxia increased me of breathing in the minority of cases whereas inter-pressure breathing consistently resulted in more marked ntilation The use of I P P B has therefore been correctly to patients with respiratory acidosis until the pH has ought to the normal level However, as previously dis-decreasing the elevated CO_2 tension so commonly present of pulmonary emphysema to a lower level is not advan-in our experience if the arterial pH is normal

patients with bronchial asthma or pulmonary emphysema under a continuous pressure of 4 to 8 cm H_2O the dyspnea tient is generally relieved Despite the fact that the func-

tional residual air is increased which in itself calls for increased ventilation, measurement of the minute volume of breathing is at times lowered In addition to the physical aid to inspiration, C P P B presumably results in a better diffusion of oxygen and carbon dioxide because of the widened diameter of the smaller bronchi maintained during the expiratory cycle. With the joint use of a continuous pressure of 6 cm H_2O and the head-down position, the pulmonary ventilation is markedly lowered as compared to the record obtained sitting erect Stimulation of proprioceptive reflexes is probably of little importance in this connection Richards takes a similar position in respect to the heightened ventilation found in cardiac failure, "The increased tachypnea and hyperpnea in advanced heart failure raises again the question of reflex factors in lungs, great vessels or elsewhere, but again the marked and consistent relief obtained by oxygen therapy brings us back to a basic chemical control Cardiac asthma, sometimes truly asthmatic in form, is still basically an acute pulmonary congestion Although it may respond to bronchodilators, its relief more often depends upon the use of oxygen, frequently with positive pressure, upon digitalization, sedation, and diuretics"

The tank respirator is commonly employed for the purpose of maintaining artificial respiration in cases of respiratory paralysis due to poliomyelitis and other neurologic diseases. Although it has also been employed in the treatment of hypoventilation in patients with pulmonary emphysema, there is always the hazard that the patient's cycle of breathing may not coincide with that of the apparatus, as will be discussed by Cherniack in the treatment of the respiratory acidosis (Chapter 14). It is pertinent to this discussion to point out that intermittent pressure breathing, accomplished by the production of negative pressure surrounding the body in the tank respirator, produced physiologic effects similar to those achieved by intermittent pressure breathing, with positive pressure applied to the upper respiratory passageway by a mask or the dome of the respirator, provided that the shape and mean pressure of the ventilatory curve are comparable Although this view has been contested by some investigators, recently by Bancroft and Wilkes, comparative studies on both types

of intermittent positive pressure breathing revealed similar changes in the volume of breathing and the venous return, according to the investigations of Maloney, Whittenberger and associates which were, in my opinion, satisfactorily confirmed in our clinic by Beck and his colleagues

Continuous positive pressure breathing of 5 to 8 cm H_2O may be carried out in the tank respirator by the use of a blower that maintains a constant negative pressure in the body compartment of 5 or 8 cm of water Pressure breathing maintained in this way, as well as in the helium oxygen hood, provides a comfortable and effective method of relieving obstructive dyspnea due to lesions in the tracheobronchial tree, as well as the dyspnea occurring in patients with pulmonary emphysema, bronchial asthma and also, to a considerable extent, in cases of left ventricular failure When the pressure is maintained with little or no fluctuation between inspiration and expiration, it is surprising to observe that patients are not aware of the effort of breathing, even during the expiratory cycle Contrary to some reports, continuous pressure breathing is not fatiguing in clinical practice, furthermore, it frequently enables the orthopneic patient to lie supine without discomfort In fact, intermittent pressure breathing devices that maintain a comparable mean pressure are in our experience not as subjectively pleasant to the asthmatic or emphysematous patient as C P P B with the methods outlined above Finally, premature bronchial closure appears to be less apt to take place in patients with pulmonary emphysema when the pressure is maintained at 6 cm H_2O during expiration and inspiration than when it drops to the atmosphere as in I P P B The spirometric measurements in a patient with severe pulmonary emphysema, seen in Figure 2 11, reveal the effect of 6 cm when applied as negative pressure around the body enclosed in a tank respirator It will be seen that a reduction in minute volume of breathing took place from 11 5 to 10 5 liters per minute in changing from the supine position to the supine position with a continuous positive pressure breathing of 6 cm A further decrease to 8,700 cc occurred when the head-down position was combined with continuous positive pressure breathing In the latter instance a considerable decrease in

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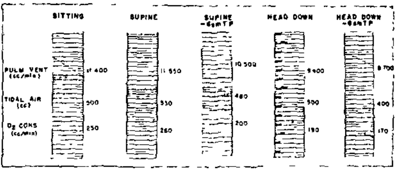


FIG 2 11 Effect of continuous positive pressure breathing in a patient with pulmonary emphysema When continuous positive pressure breathing was obtained by providing a negative pressure of 6 cm of water in the body compartment of a tank respirator in the supine position, the ventilation decreased from 11 5 to 10 5 liters per minute. When this pressure was exerted at a headward tilt of the thorax of 10° the ventilation dropped further to 8 7 liters per minute. The effect of diaphragmatic breathing produced by the head-down position alone was manifested by a decrease in pulmonary ventilation from 11 5 to 9 4 liters per minute with a decrease in oxygen consumption from 260 to 190 cc. per minute.

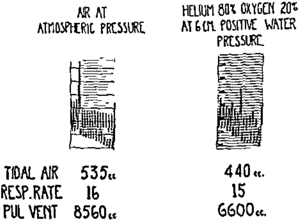


FIG 2.12 A decrease in pulmonary ventilation took place from 8,650 cc breathing air to 6,600 cc. per minute when the patient breathed 80 per cent helium with 20 per cent oxygen at a continuous pressure of 6 cm H_2O Diagnosis Partial obstruction of left main bronchus (Barach, A. L, J A M. A, **107:** 1273, *1936*)

oxygen consumption took place, namely from 260 to 170 cc per minute. The change from costal to diaphragmatic breathing as produced by headward tilt of the thorax of 18° resulted in itself in a decrease in minute volume of breathing from 11 5 to 9 4 liters

In 1936 when the joint effect of inhalation of 80 per cent helium with 20 per cent oxygen with 8 cm H_2O C P P B was tested in a patient with pulmonary emphysema, the reduction in ventilation then recorded was from 15 7 to 10 6 liters per minute, a result similar to the effect of inhaling 100 per cent oxygen The decrease in ventilation accomplished in a patient with partial obstruction of the left main bronchus yielded a similar result As seen in Figure 2 12, the pulmonary ventilation decreased from 8,560 cc to 6,600

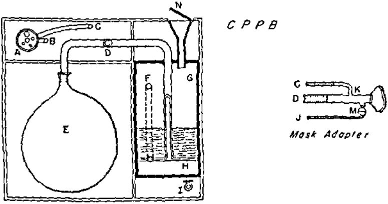


FIG 2 13 Diagram of continuous pressure breathing apparatus, indicating use of elastic rubber bag and perforated metal can as expiratory valve (Made by OEM Corp, East Norwalk, Conn)

A Oxygen-air injector, B, Oxygen inlet C Oxygen-air outlet to mask D Pressure line from pressure accumulator to mask, E Pressure accumulator (rubber balloon) F Sight gauge calibrated in C M of water pressure at the mask G Water tight brass tank H Perforated brass plate to diffuse expiratory air bubbles and reduce water level excursion I Drain valve for draining tank and adjusting pressure level J Oxygen to nebulizer K Mask-tubing-nebulizer fitting L Face piece with cushion M Nebulizer for introduction of aerosols, N Filler pipe and air vent Open while in use, sealed when transporting

cc when the helium oxygen mixture, administered with continuous pressure breathing, was substituted for air. The ventilation with 100 per cent oxygen was 7,380 cc per minute.

The mask continuous pressure breathing device formerly used in our clinic is not as satisfactory as a recently developed apparatus in which the elastic force of a distensible rubber bag is employed to provide an even pressure throughout the respiratory cycle By *means of an injector used at a setting of 33 per cent* oxygen, an inspiratory flow of 10 liters per minute of oxygen draws into the mask an additional 60 liters of air. Expiration takes place under water through a series of small holes in a perforated metal can. It was emphasized previously that a slight increase in the inspiratory oxygen pressure results in a relatively large increase in arterial oxygen saturation in severely hypoxic patients with pulmonary emphysema because of the steep slope of the oxygen dissociation curve of hemoglobin in the presence of the severe degree of oxygen want frequently found in these cases During the administration of air with continuous pressure *breathing the dyspnea is relieved as a consequence of the improved* diffusion of oxygen and carbon dioxide but greater alleviation of hypoxia may be expected with the employment of either 33 or

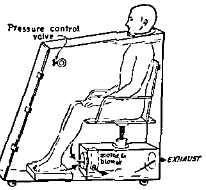


FIG 2 14 Sitting up chamber for study of continuous positive pressure breathing maintained by maintenance of a negative pressure of 2 to 10 cm surrounding the body (Made by Respiration Aids, 424 East 123rd St, New York, N Y.)

40 per cent oxygen atmospheres Even more complete relief of obstructive dyspnea would be provided by inhalation of 80 per cent helium with 20 per cent oxygen With the use of the latter gas the injector is closed and the oxygen regulator set at 15 liters a minute, which would result in a flow of 26 liters of the helium-oxygen mixture A pressure setting of 5 to 6 cm of water may be found useful for most cases, but this can be varied to suit the needs of the individual patient For optimal maintenance of continuous pressure a flow of not less than 7 liters per minute is required at the 33 per cent and 10 liters per minute at the 40 per cent oxygen setting. The continuous pressure breathing device is illustrated in Figure 2 13 A sitting up box by which positive pressure breathing may be studied through the maintenance of 5 to 8 cm negative pressure in the body compartment is illustrated in Figure 2 14

A selective bibliography is given on page 324

Chapter 3

RESTORATION OF DIAPHRAGMATIC FUNCTION AND ALLIED BREATHING EXERCISES

ALVAN L BARACH, M D

Attempts to enhance diaphragmatic breathing in patients with pulmonary emphysema by deliberate training have been carried out intermittently since the time of Saenger and Hofbauer However, it should be recognized that the diaphragm itself is not diseased, except that inadequate use predisposes it to atrophy. A more accurate description of this therapeutic objective is restoration of pulmonary function since the failure of diaphragmatic ascent is due to impairment of elastic recoil of the lungs in expiration, which is in turn dependent on obstructive bronchiolar trapping of air, alveolar overdistention and the resultant depression of the dome to a lowered position The diaphragmatic muscle still may be seen to contract in inspiration, as evidenced by the retraction of the lower costal margins of the thorax, but its ventilatory effectiveness is largely lost until measures are instituted whereby its upper surface is elevated and restored to a convex shape These measures enhance in varied ways the relaxation pressure of the lung, which permits the diaphragm to function more normally, hence the phrase, "restoration of diaphragmatic function," in essence refers to restoration of the recoiling activity of the lung itself

Some confusion has perhaps arisen because expiration has been termed a "passive" act When the diaphragm and the intercostal muscles relax, ascent of the diaphragm into the chest is normally brought about by a negative pressure produced *through the recoiling* force of the lungs; the intrapleural pressure between the

lower lobes of the lung and the upper surface of the diaphragm becomes increasingly negative at the end of inspiration, as a result of which the diaphragm is lifted during expiration with the abdominal contents attached to it, namely liver, spleen and omentum. Thus, in normal respiration, expiration follows relaxation of the inspiratory musculature but the contraction of the elastic elements of the lung overcomes the gravitational force of the organs attached to the diaphragm. In patients with pulmonary emphysema in whom elastic recoil of the lung is impaired, the expiratory intercostal and abdominal muscles assist the process of exhaling air, but this is a less efficient mechanism than when the recoiling pressure of normal pulmonary parenchyma accomplishes deflation of the thorax.

Since overinflation of the lung in pulmonary emphysema results directly in a depressed diaphragm, the lower lobes and the hilum will not only be inadequately ventilated but may also be the source of rebreathing with the overexpanded upper portion of the lung, especially when the diaphragm paradoxically moves upward as a result of forceful inspiratory contraction of the muscles of the upper thorax, neck and shoulder girdle.

Descent of the diaphragm in the normal individual is accompanied by contraction of the lower intercostals with the result that the upper abdomen generally manifests a protrusion and the lower ribs are flared outward at the end of inspiration. In severe pulmonary emphysema when the ribs are pulled inward by the diaphragm despite contraction of five of the lower inspiratory intercostal muscles, the force of the compensatory expansion of the upper thoracic cage with elevation of the shoulder girdle is then transmitted directly to the alveoli at the periphery which are overventilated at the expense of the more normal lung tissue at the hilum.

Serious impairment of diaphragmatic (or lung) function also takes place as a result of other factors than anatomic emphysema, both in patients and otherwise normal individuals. Heckscher has emphasized that a marked diminution or loss of diaphragmatic movement is characteristically observed in soldiers who stand with shoulders thrown back and the "guts" sucked in, this military

posture in itself results in hyperinflation of the lungs, flattening and tensing of the abdominal musculature, with impairment of its descent on expiration, and an increase in residual air. Gymnastic instructors teach exercises for the purpose of increasing chest expansion and frequently advocate an erect lordotic posture with similar consequences. The diaphragm has also been found to be unusually low in women with hysterical pregnancy and in others who suffer from a syndrome described as periodic abdominal distention not associated with flatulence. Excessive upper thoracic respiration has been observed in a motion picture actress, adopted for its scenic effect, with the result that little or no diaphragmatic motion was seen on fluoroscopy in the standing position. Patients with the hyperventilation syndrome are also costal breathers, the periodic sigh or deep breath being consistently performed with a characteristic upward motion of the thorax and accessory neck muscles, similar to the chest heaving of cases of pulmonary emphysema.

In some patients with poliomyelitis who have had respiratory paralysis three months to a year or more previously, the failure to employ diaphragmatic respiration is not entirely due to central nervous system involvement. Pressure of the hand or the application of an emphysema belt below the umbilicus was found in some cases to produce a conspicuous decrease in the volume of pulmonary ventilation as well as a marked reduction in upper thoracic and accessory neck muscle respiration with a sensation of diminished effort of breathing. In these instances, the lungs of the patient perform as if some degree of impairment of elasticity took place during the acute phase of poliomyelitis, since a slight elevation of the diaphragm resulted in a perceptible increase in its motion with a significant improvement in the efficiency of respiration.

That diaphragmatic respiration was superior in ventilatory effectiveness to that of the chest musculature, was described more than a century ago by Astley Cooper and Duchenne. In 1909, Keith stated that the lower lobes of the lungs were expanded mainly by diaphragmatic excursion, but he did not mention at that time movement of the hilum as a result of diaphragmatic

respiration Howkins, recognizing the interference with diaphragmatic motion exerted by the downward pulling pressure of the visceral organs attached to the undersurface, recommended the supine rather than the sitting-up position as a method of lowering the incidence of chest complications, he reported a 60 per cent reduction of the vital capacity with a complete immobility of both leaves of the diaphragm The headward tilt of the thorax naturally still further aids the recoil of the lungs by the weight of the viscera which presses upward on the diaphragm With the decrease in the volume of the thoracodiaphragmatic cage, the pulmonary ventilation is then characterized by increased movement of the reserve air, both in normal subjects and those with pulmonary emphysema and bronchial asthma

Reich was the first to make the observation that introduction of air into the peritoneal cavity at a pressure sufficient to elevate the diaphragm 3 cm resulted in a corresponding increase in its excursion, with simultaneous relief of shortness of breath The value of this procedure, confirmed by a number of investigators, is still strongly advocated by Banyai Kountz and Alexander, Christie, and Gordon found that a somewhat similar result was obtained by physical pressure applied to the lower abdomen, either by the flat of the hand or by a specially designed belt A basic physiologic effect of any procedure that provides a dome shape to the diaphragm and maintains it at a higher level in the chest is an increase in the range of its motion, provided that the pressure attained in the abdominal cavity is not so high that the diaphragm cannot contract against it In patients who respond to these measures with increased diaphragmatic movement, the intrapleural pressure is altered in the direction of higher negativity, thus, instead of a range of plus 2 to minus 4 cm H_2O during a quiet expiration and inspiration, the intrapleural pressure may be found to be minus 2 to minus 5, a comparable fall in systemic venous pressure takes place in these cases However, when the venous pressure rises above the control value after pneumo-

here that the patient with emphysema may require specific training in using the diaphragm to take advantage of procedures which elevate it, since upper thoracic costal respiration may persist as a habit until it is deliberately broken. Perhaps it would be better to say that the patient requires an orientation by training which transfers the use of the intrapleural negative pressure to the bases rather than exclusively to the upper periphery of the lung.

With the decrease in lung volume produced by elevation of the diaphragm, a reduction in functional residual air is found, as well as an increase in alveolar ventilation, especially of the parts of the lung that are inflated by contraction of the dome of the diaphragm, *i e*, the lower lobes and hilum An increased effectiveness of the cough is in part dependent on better aeration of the dependent areas of the lung An increase in the relaxation pressure of the lung is a direct result of any increase in intra-abdominal pressure which offsets the gravitational force of the liver and spleen

A lowering of the minute volume of breathing is a good indication of the increased efficiency of ventilation initiated by raising the dome of the diaphragm, this response is more marked with the employment of the headward tilt of the thorax than with either pneumoperitoneum or the use of the emphysema belt, especially since Beck and I have shown that diffusion of oxygen and carbon dioxide is not impaired even with a 20 to 30 per cent decrease in pulmonary ventilation In the leaning-forward position, either standing or sitting in a chair, the downward pull of the viscera is decreased but lung volume is in this instance increased, in part due to the falling away of the mediastinum from the posterior parts of the lung Of four patients with pulmonary emphysema in whom the immediate response to leaning forward 35 degrees was tested, the pulmonary ventilation showed an average decrease of 13 per cent in two and 3 per cent in the remaining two cases. The combined effect of the belt and the leaning-forward position is illustrated *in Figure 3 1 in which it is seen that there was a decrease* in pulmonary ventilation from 14,400 to 8,500 cc per minute The decreased minute volume of respiration was made possible by redistribution of air to better preserved parts of better perfused

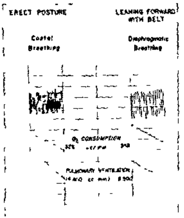


Fig 3 1. The pulmonary ventilation breathing air was lowered from 14,400 to 8,500 cc as a result of the change from the erect to the leaning forward posture together with the application of a G -B. emphysema belt As a result of the combined procedure, costal breathing was altered to a predominantly diaphragmatic respiration (Barach, A L, Arch Phys Med & Rehab, 36: 380, 1955)

lung, the result of increased diaphragmatic breathing The slowing of the velocity of air flow also lessens the operation of the check valve mechanism characteristic of bronchial constriction It will be evident in other chapters that high rates of air movement are accompanied by increased trapping of air, increased turbulent flow and decreased compliance, especially in the erect sitting or standing position which predisposes the patient to the kind of ventilation that is applied to the peripheral more diseased areas, because of exaggerated expansion of the upper thoracic cage

The importance of attempts to restore diaphragmatic function by deliberate training in breathing was clearly recognized by Hofbauer who was responsible for a program aimed to facilitate ascent of the diaphragm by deliberate contraction of the abdominal musculature at the end of expiration, a procedure subsequently employed in the main by Livingstone and, more recently, by Allan, M E Miller, Becklake and associates, Fein and associates, W F Miller and others Heckscher, however, believed that the use of the leaning-forward "easy-standing" posture was a more reliable method of maintaining diaphragmatic respiration

than expiratory contraction of the abdominal muscles; the latter procedure was criticized by Christie as an unnatural practice

The Hofbauer technique has not been generally employed in the treatment of our patients Although expiratory contraction of the abdominal musculature and lower intercostals can be observed at rest, and at times is employed unconsciously during walking, deliberate practice with this method has not resulted, in our hands, in as much benefit during exertion as training in accentuating the normal process of lung recoil and diaphragmatic contractions With the use of the supine and the head-down positions, in which the gravitational force of the viscera is less of a handicap to the relaxation of the lungs, a more natural breathing habit has been inaugurated in the majority of 500 patients treated in the past ten years The use of diaphragmatic respiration during walking, especially when in an erect posture, is physiologically difficult The patient is therefore encouraged to stand in the leaning-forward position and to wear an emphysema belt, since the lungs are then in an improved position to facilitate increased ascent and consequently effective movement of the diaphragm. Patients carry on upper thoracic breathing partly because of the characteristic pulmonary distention, but also as a habit which seems to have developed during periods of acute dyspnea and overinflation of the lung and maintained in part by a posture not suitable to their mechanical breathing disorder The habit component may be abandoned after instruction and practice as mentioned above, the relief of alveolar distention is attempted by the various therapies presented in this volume

When the patient is tilted head down, with the thorax inclined at an angle of approximately 20°, the abnormal distribution of ventilation may be seen to change in the direction of normal by the prompt abandonment of the use of the accessory muscles of respiration The superficial and relatively functionless distended air-sacs, which in the erect position are overventilated, fill earlier than the deeper parts, since traction is directly applied by the expanding chest wall, and bullous areas interpose little resistance at the start of inspiration Since the headward tilt of the thorax results, either spontaneously or after instruction, in a prompt

abandonment of this type of upper costal breathing, the more normal alveoli around the hilum are now aerated, the intrapleural negative pressure in the region under the lower lobes is aided by the increased (visceral) intra-abdominal pressure A better overall perfusion of the lungs also takes place, due to the effect of gravity on blood entering the lung from the abdomen and the restored rhythmical contractions of the diaphragm, furthermore, the more normal lung tissue at the hilum is itself possessed of a more intact capillary circulation

Since the surface area of the diaphragm is approximately 270 sq cm, a gain of 2 cm in its total excursion would theoretically represent 540 cc tidal air If the increased movement were mostly confined to the dome and we were to estimate this surface as one-half the total area, a selective ventilation of 270 cc would thereby be produced in the better functioning elements of the lung Since any procedure which raises the diaphragm offers the patient the advantages of a highly efficient redistribution of air in the lungs, similar effects might be expected by a suitable elastic emphysema belt and by pneumoperitoneum Furthermore, physiologically directed therapeutic procedures such as inhalation of bronchodilator aerosols for relief of bronchospasma and manual compression of the chest may also contribute to better diaphragmatic function by decreasing lung inflation, provided the patient has been trained to take advantage of any decrease in pulmonary overdistention through diaphragmatic breathing Although elevating the diaphragm results in a decrease in lung volume, which theoretically tends to decrease bronchial diameter proportionately, the behavior of the patient indicates that trapping of air is not produced Deflation of the lung not only diminishes the functional residual air and increases alveolar ventilation but it would also appear that the bronchiolar walls through which ventilation now takes place are less susceptible to collapse, that the pressure on their external surface is now less in comparison to the airway pressure, perhaps due to a more efficient recoil of the elastic elements attached to hilar and lower lobe lung tissue and in part to the decreased velocity and volume of respiration initiated primarily by the more efficient ventilation

Although a number of observers have reported clinical benefit following diaphragmatic training, the response of the series of patients mentioned by W. F. Miller included also an increase in vital capacity, maximal minute ventilation, arterial oxygen saturation, at rest and immediately after exercise, as well as a small but possibly significant decrease in arterial pCO_2, both at rest and after exercise. The most striking of the functional evidences of benefit by diaphragmatic breathing was demonstrated in the blood gas studies on patients tilted into head-down positions

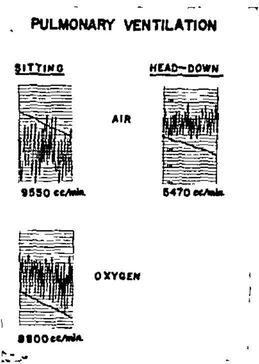


FIG. 32 A graphic record of pulmonary ventilation is shown in a patient [illegible] volume of [illegible]0 cc when [illegible] was accompanied by a change from an exclusively costal to a diaphragmatic type of respiration. There was, in addition, a slight decrease in pulmonary ventilation during the inhalation of 100 per cent oxygen although clinical evidence of pulmonary emphysema was absent.

since diffusion of oxygen and carbon dioxide was maintained even though a marked lowering of the total minute volume of breathing occurred promptly after disappearance of the upper costal respiration, these results, which will be commented upon by Beck in the chapter on bronchial drainage (Chapter 7), illustrate to what extent the faulty distribution of air in pulmonary emphysema can be overcome Although Wade did not find that diaphragmatic training, as carried out in England, resulted in a greater movement of the diaphragm *during a maximal inflation of the lung*, his data do not support this conclusion during moderate breathing, nor do they appear to be relevant to the problem of the patient with pulmonary emphysema in whom forced ventilatory excursions are not only contraindicated clinically, but also result in pathophysiologic events, such as air trapping, that are well known to produce alveolar overdistention Fluoroscopic examination of a patient on a table tilted to the degree required to initiate diaphragmatic motion reveals the abdomen protruding during inspiration, as it does in the head-down position in a bed and a tilting chair, or in the leaning-forward position

Although a comparison of the pulmonary ventilation with the patient sitting erect and head down is a sensitive characteristic indication of pulmonary emphysema in most cases, marked reduction of ventilation may occur in people who suffer from the syndrome of hyperventilation on a psychosomatic basis In Figure 3 2 the pulmonary ventilation of a patient with chronic bronchitis and anxiety neurosis decreased from 9,550 to 5,470 cc per minute when his thorax was tilted headward, accompanied clinically by a disappearance of the characteristic sighing movements of the upper thorax and shoulder girdle The decrease in the ventilation breathing 100 per cent oxygen, ordinarily interpreted as a manifestation of the presence of impaired pulmonary diffusion of oxygen, was in this instance not considered diagnostic of pulmonary emphysema because of the highly irregular quality of the ventilation

At the start of the training of the patient he is first of all told *that he is not expected to learn the various procedures in the* first session! A few details of the instruction procedure will be

given. The supine position may be employed with the pressure of one's hand on the abdomen but the quickest and most effective method is to use the headward tilt of the thorax to produce diaphragmatic excursion Two pillows are inserted under the head to prevent flushing of the face. The angle desired, between 16 and 25 degrees, may be determined in various ways, including tilting of the fluoroscopy table with observation of maximal diaphragmatic movement, the Colby chair, an angle-iron board, the foot end of the gatch bed or the hydraulic bed lifter.* The physician places one hand on the chest and the other on the abdomen to demonstrate the onset of alteration in the character of his breathing When protrusion of the abdominal wall takes place during inspiration, the hands of the patient replace those of the physician in order to clarify the procedure further. He is encouraged to dispense altogether with movement of the upper chest and to breathe as little as possible. Decreased sensation of dyspnea and a diminished volume of breathing are noted generally by the patient as well as the physician or therapist. The patient is instructed to carry on a similar practice at home for one-half to one hour three times daily

The patient is then asked to continue diaphragmatic respiration lying supine, generally with the help of a 10- to 15-lb. sandbag on the abdomen, which increases the intra-abdominal pressure and thereby elevates the diaphragm The sandbag may also be used in this position at home as an exercise for the diaphragmatic muscle itself. When the patient resumes the standing position, the costal breathing is apt to return promptly. He is now told to lean far forward with his hands against the upper abdomen until he can tell that diaphragmatic breathing is taking place by an anterior movement of the hands in inspiration. In certain cases he may have to bend until his chest is almost perpendicular to the pelvis in order to demonstrate an unquestionable diaphragmatic motion, under these circumstances the relaxation pressure of the

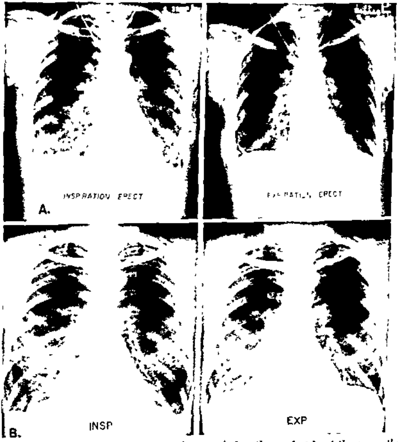
* Made by Du Puy or Zimmer Co, both in Warsaw, Indiana A comfortable, [illegible] table, [illegible] a head rest and [illegible] blood

lungs is much increased since the diaphragm moves in a horizontal direction, and the gravitational force of the viscera is directed vertically downward. When abdominal breathing has been adequately demonstrated the patient gradually straightens up to a somewhat more upright position, at the same time attempting to preserve diaphragmatic movement. In the fully erect posture the patient will revert again to costal breathing and he should be then encouraged to lean forward slightly, both in standing and in walking, although the head itself need not be inclined downward. In Figure 3 3, x-ray illustration of diaphragmatic breathing is revealed in 4 patients after at least three months training, the excursion from full inspiration to full expiration was photographed in the standing position.

During the various training procedures hyperventilation is avoided. The patient is told explicitly and repeatedly to breathe as little as possible, to avoid deep breaths as well as the use of the upper chest, the shoulder girdle and neck muscles. Exertion should be stopped when puffing begins, and the leaning forward position immediately instituted until breathing becomes quiet. Unfortunately, either through anxiety or improper early training, expansion of the chest has been practiced deliberately in many instances far beyond the ventilatory requirement of the individual. A special effort should be made to talk slowly. Other activities which are also apt to provoke dyspnea, such as raising the shoulders and lifting the hands to the face, as in shaving or combing the hair, are better performed in a leaning-forward posture, whether sitting or standing.

In the same session or on the following day, the patient is taught to use an emphysema belt. In order to make clear to him that a very real benefit will follow wearing a support of any kind, he is instructed to walk, or exercise on a two-step test, until shortness of breath occurs. The physician then stands behind him, bends his thorax forward to facilitate diaphragmatic breathing and holds the lower midabdomen upward and inward with a gentle but firm pressure. A sensation of subjective relief of dyspnea will be experienced by almost all patients with pulmonary emphysema, provided that some degree of diaphragmatic respiration is

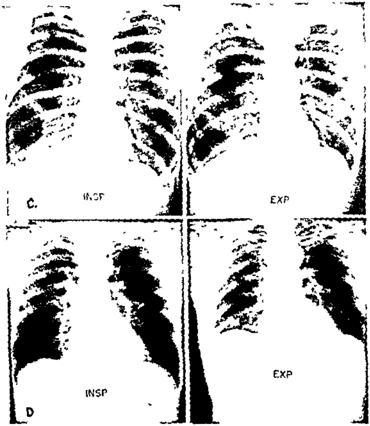
being employed The bending forward position is utilized since the continuance of the exaggerated movements of the thoracic cage for the purpose of ventilation will *prevent the objective* desired through the application of manual pressure, namely, overcoming the downward pull of the visceral attachments to the diaphragm



...onths'

...tic movement indicated by the change in position of the upper surface of the diaphragm to the 11th rib on the right side

Case B A man with pulmonary emphysema and pulmonary fibrosis In case A and B the diaphragm *is flattened on inspiration. (See cases* C *and* D *following*)



Case C In this case with advanced bullous disease of the lower lobes, maximal diaphragmatic movement was inadequate to relieve dyspnea in either the standing or erect sitting position Despite 3 months' of training and use of the G-B belt, the patient was short of breath except when supine, head down, or breathing nasal oxygen sitting

Case D A patient with bronchial asthma and pulmonary emphysema The marked degree of ascent of the diaphragm at the end of expiration was accomplished with the aid of contraction of the abdominal musculature

In each of these patients the use of the diaphragm was also manifested on fluoroscopy In the relaxed slightly leaning-forward position little use was now made of the accessory muscles of respiration in cases A, B, and D which was in contrast to the prominent upward and forward movement of the chest previously accomplished by contraction of the upper intercostals the muscles of the neck and shoulder girdle

Although the principles of the emphysema belt were outlined long ago and indeed effectively applied by Alexander, Kountz, Kerr and others, the slight modifications introduced in the so-called Gordon Barach Emphysema Belt render it a more effective device for increasing intra-abdominal pressure; the elastic bands also store energy during inspiratory descent of the diaphragm which subsequently aids the recoil of the lungs on expiration The belt is attached below the umbilicus so that no interference with an inspiratory widening of the chest diameter with flaring of the lower ribs is produced as a result of contraction of the lower intercostals as well as the diaphragm. The attachment of the belt* is illustrated in Figure 3 4 The belt is ultimately worn continuously from the time of arising to retiring. The pressure applied is moderate in degree at first and later increased by tightening the straps In women and thin men a soft upper band is used for greater comfort and to prevent its bulging through the clothes. It is necessary for some degree of diaphragmatic movement to take place in order to secure the therapeutic advantages desired For that reason the patient is generally advised to lean forward frequently, at an angle of 15 to 45°, until abdominal breathing is a more or less unconscious habit In many instances the standing *erect* posture can never be achieved with the full benefit desired from the wearing of an emphysema belt As the diaphragm becomes stronger as a muscle, tightening of the belt over the lower abdomen may be increased since a higher intra-abdominal pressure will tend to further aid elastic recoil of the lungs. In a patient in whom x-ray studies were made on the effect of posture on maximal excursion of the diaphragm, it was found that the average descent of the right and left anterior leaves of the diaphragm was 2 0 cm in the standing position, 3 6 supine and 5 3 head down at an angle of 16 degrees Had the patient with pulmonary emphysema preserved an original inclination to walk on all fours, the belt would be a less necessary item Under the circumstances of ambulatory activity, however, excursion of the lower parts of the lung and hilum are maintained by this method of aiding the

* *Manufactured by the Spencer Co , New Haven, Conn*

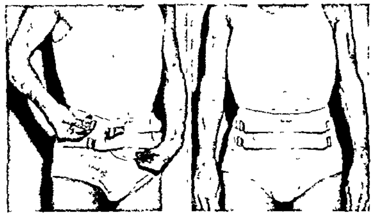


FIG 3 4 This light abdominal support contains two spring metal bands attached to a pad placed below the umbilicus The lower band is stronger and designed to increase the intra-abdominal pressure and raise the abdomen Both bands store mechanical energy during inspiratory descent of the diaphragm, aiding recoil of the lungs during the expiratory cycle In women a soft upper band is used to prevent bulging of the device through the clothes In thin men the soft upper band is also employed

recoiling pressure of the lung, which, from a physiologic point of view, is better applied to the surface of the diaphragm than to the periphery of the upper lobes A sandbag of 10 to 15 pounds in weight is also frequently employed as a method of increasing the intra-abdominal pressure and of providing exercise of the diaphragmatic muscle Used in the evening at bed, it is at times helpful in counteracting dyspnea

An elastic vest has been used in our clinic to restrict as well as to aid upper thoracic motion but in most cases subjective comfort during the application of pressure was not achieved However, it seemed to us both on theoretical grounds and in clinical practice, that some benefit did take place by reason of the compression of the thorax exerted by the sponge rubber or elastic tissue during the expiratory cycle

Various attempts to decrease lung volume have been employed in patients with pulmonary emphysema, including manual pressure to the abdomen and air pressure applied by cabinets during

the expiratory cycle. A maneuver which is readily taught to the patient by the physician consists in manual compression of the lower ribs and upper abdomen, generally carried out immediately after inhalation of a bronchodilator aerosol from a nebulizer. The purpose is both to squeeze excess air out of distended alveoli and to propel mucus from the dependent parts of the lungs and the smaller bronchi into the upper respiratory tract. The hands are placed on the anterolateral surface of the lower ribs and the upper abdomen. The position may be determined by leaving a hand's length space between the two hands which are then used, fully extended and not bent, to compress the lower thorax during the latter half of expiration If the fingers are kept straight and rigid an uncomfortable degree of pressure will not be applied to the abdomen This maneuver is carried out either on ten consecutive expirations or on alternate expirations, it should include three or four sharp, abrupt, vigorous compressions of the thorax Wheezing may become audible during expiration as well as loud ronchi until the mucus is expectorated

Deliberate coughing is advocated whether or not it spontaneously develops after inhalation of nebulized epinephrine and manual compression of the chest The coughing effort should not be violent because a too forceful cough results in the development of premature closure of the bronchioles as a result of too high intrapulmonary pressures Evidence of mucus remaining in the chest will often be noted by the presence of gurgling sounds and the patient may not bother to cough unless deliberately instructed to do so Manual compression of the chest is advised three times daily and at other periods when as a result of exertion the patient feels dyspneic and presumably has developed over-distention of the alveoli The vital capacity may show an increase of 200 to 800 cc immediately following this maneuver but a better result is generally obtained when the procedure follows inhalation of a bronchodilator aerosol. The effect of manual compression is illustrated in Figure 3 5 in which it is seen that the vital capacity was moderately increased after manual compression from 1,000 to 1,350 cc but was still further increased when manual compression followed the inhalation of 2 25 per cent racemic epinephrine, namely,

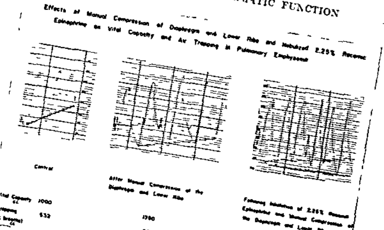


Fig 3 5 Manual compression of the thorax and upper abdomen resulted in diminished dyspnea, a decrease in the trapping of air after three breaths from 532 to 290 cc, and an elevation in vital capacity from 1,000 to 1,350 cc A still further improvement was manifested when this procedure was done after inhalation of a bronchodilator aerosol (0 5 cc Vaponefrin) Trapping of air was then absent and the vital capacity rose to 1 500 cc (Barach A L, Am J Surg, 89, 376, 1955)

o 1,500 cc Furthermore, during the control period deep breathng resulted in the trapping of 500 cc of air whereas following he final procedure deep breathing took place without any air apping The symptomatic result was marked relief of dyspnea, th at rest and on walking

The effect of squeezing the lower chest in expiration results in increased tidal air and a somewhat less marked increase in l minute volume In 10 cases of poliomyelitis with moderate urment of respiratory function, the mean increase in tidal as 40 per cent, with a decrease in pulmonary ventilation of r cent The more efficient alveolar ventilation was reflected spontaneous lowering of respiratory rate of 3 7 breaths per e

b squeezing apparatus is being currently studied in which ble balloons are placed over the lower anterolateral surface

of each chest A motor-blower unit is employed to transmit pressure during the latter half of expiration. An increase in tidal air similar to that achieved by manual compression is obtained The increased movement of the reserve air provided in this way appears to be an aid to ventilation in subjects with moderate impairment of respiratory function and, in patients with pulmonary emphysema and an associated productive bronchitis or bronchiectasis, seems *to aid the expectoration of bronchial secretions*

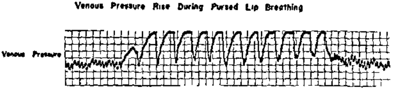
Pursed Lip Breathing

The physiologic and clinical aspects of pursed lip breathing are of considerable interest Hofbauer and Shutz advocated the use of a whistling or humming sound made by the patient during expiration for the relief of dyspnea in cases of bronchial asthma and pulmonary emphysema Livingstone instructed the patient to make an F-sound during a long expiration following a quiet inspiration Patients with pulmonary emphysema are frequently seen in whom pursed lip breathing has been spontaneously adopted In addition, this maneuver has been observed in stone cutters in Italy and lumberman in Canada as well as in mountain climbers in various parts of the world during periods of strenuous exertion In our clinic, a full inspiration is recommended followed by a slow expiration against the pressure induced by constricting the lips, the degree of pressure being generally increased as dyspnea itself is more severe

The maintenance of this form of expiratory pressure breathing when the lungs are in a more expanded state results in air-flow through more patent bronchi than would be the case with a small or so-called quiet inspiration, it will be remembered that the diameter of the smaller bronchi was found to be *enlarged during expiration* by the application of a continuous positive pressure of 6 cm of water As expiration is concluded lung volume decreases and the expiratory flow rate diminishes markedly Although expiration is prolonged by this maneuver, in order to *deliver air* from the more diseased areas which eliminate the inspired tidal volume more slowly than the better more elastic parts of the lung, it should not be so lengthy as to result in a feeling of shortness of

breath, or in physiologic terms, to proceed to the point of bronchiolar closure and hypoxia The pursed lip exhalation is ended generally at a point in the cycle representing two thirds of a maximal expiration but in clinical practice the patient himself often decides the optimal length of the expiratory cycle. The abdominal and expiratory intercostal musculature contracts against the increased intrabronchial pressure and the diaphragm is plainly elevated by the increased intra-abdominal pressure. In fact, patients may then use a degree of expiratory abdominal contraction as an aid to diaphragmatic breathing itself If this becomes an automatic habit, it is clearly valuable More time is also allotted to the expiratory cycle, and, with a slower expiratory flow rate, check valve closure of the bronchioles is less apt to take place In fact, sibilant rales audible during asthmatic breathing frequently disappear or are markedly diminished during the period of its use Contrariwise, patients who adopt rapid respiration with the mouth open and thereby produce loud expiratory sounds are often found among those who seek disability or manifest other psychosomatic influences

When pursed lip breathing was carried out with a marked constriction at the lips in normal subjects, a rise in peripheral venous pressure of 60 mm H_2O was found during the expiratory cycle, as seen in Figure 3 6 This response was manifestly comparable to



	Control	Pursed Lip Breathing	Control
Inspiratory	80 7	92.8	81 5
Expiratory	97 6	159 6	104 5
Mean	88.5	136.2	92.3

FIG 3 6 *The mean rise of venous pressure during pursed lip breathing was* 48 mm H_2O, during the expiratory cycle the rise was 62 mm H_2O (Barach, *A L*, *Bickerman, H A*, and *Beck, G J*, *Bull New York Acad Med*, **28**: 353, 1952)

may be present It is at times helpful to make the suggestion to employ pursed lip breathing at the start of the head down position if slight dyspnea is present, until the heart accommodates itself to the increased pulmonary congestion. The augmentation of blood-flow into the lungs is temporary as the circulation after a period of time is restored to its previous cardiac output, at least in those with a normal circulatory apparatus. If dyspnea is moderately severe, the headward tilt is abandoned. In one of our patients with right and left heart failure, fluid from the right base was displaced to the apex when he was placed head down but improvement in ventilation due to redistribution of blood from the emphysematous areas to better perfused hilar regions of the lung was followed by relief of dyspnea and decrease in total minute volume of respiration, notwithstanding the transient increases in pulmonary congestion Placing two pillows under the head so that it is inclined upward is also more apt to produce a feeling of comfort in the early use of the head-down position.

The physical aids to breathing described in this section have been presented in the main from the point of view of initiating a more efficient ventilation for the relief of dyspnea, but some of these procedures will be reviewed by Beck (Chapter 7) from the standpoint of their value in the promotion of drainage of retained secretions from the lungs In our clinic it has been found serviceable to have printed directions for the patient which outline the day's program, beginning with the use of the nebulizer for the relief of bronchial spasm, followed by manual compression of the lower ribs and upper abdomen, training in diaphragmatic breathing with the head-down position, attachment of the emphysema belt, deliberate coughing and practice in pursed lip breathing In addition, exercise of the abdominal muscles is carried out in some cases The supine position is employed with upward extension of the legs, first one at a time, then both, often followed by a bicycling maneuver If dyspnea takes place, these exercises are performed during inhalation of 8 to 10 liters per minute of oxygen through the plastic nasal cannula

A selective bibliography is given on page 234

Chapter 4

SENILE EMPHYSEMA

HYLAN A BICKERMAN, M D

Most textbooks of medicine recognize senile emphysema as a distinct clinical entity and classify it under the broad heading of pulmonary emphysema Nevertheless, considerable differences of opinion exist as to whether senile emphysema represents true pathologic alterations in the lung itself or the structural changes of senescence which may be mistaken for pathologic degeneration. In his original description of emphysema, Laennec did not include senile emphysema and he did not consider the senile lung as a form of emphysema This view was also taken by Landis who stated "In the strict sense of the word, this is not a true emphysema at all it is but one of the atrophic changes commonly met with in the aged "

On the other hand, Rappaport and Mayer consider the essential pathogenesis to be identical in both hypertrophic and senile emphysema, the main differences being in gross appearance Richards prefers to distinguish between a mild form of senile emphysema representing a normal aging process in which the pulmonary tissues suffer some loss of elasticity and resiliency similar to other tissues, and a pathologic form with "marked loss of elastic tissue, degeneration of alveolar walls and diffuse coalescence of alveolar spaces, producing in extreme cases a typical honeycomb lung " With such differing concepts, it is no wonder that other descriptive terms such as, nonobstructive, postural, atrophic, and "small-lunged" have been used interchangeably with senile emphysema

Alterations Occurring in Senescence

Since the problems of old age and disease, although not identical, are oftentimes so intermingled that it becomes impossible to distinguish between the depreciations which occur in the older individual due to senescence and those due to pathologic processes, a review of the changes in the lung and its supporting structures as a result of aging would help to clarify some of the divergent opinions expressed above

The Thorax

Ventilatory efficiency is dependent in part upon the highly integrated activity of the muscles, joints and bony skeleton comprising the thorax It is apparent that any structural change in the thorax accompanying the aging process could conceivably alter respiratory function The aged person is typically pictured as assuming a stooped, bent-over posture This position has been attributed to a weakening and relaxation of the back musculature together with changes in the vertebral column As early as the fiftieth year, Vischer found a measurable diminution in body stature due to alterations in the intervertebral cartilages which grow thinner, smaller and drier

In considering the bony and cartilagenous elements of the thoracic cage, much emphasis has been placed on changes occurring in the intervertebral discs Warthin described the typical senile thorax as having a short, sharply curved spinal column with contracted and thinned intervertebral discs The thorax was barrel-shaped with a wide epigastric angle More recently, Takahashi and Atsumi reviewing the changes in thoracic form with age in 9,369 Japanese noted that the chief cause of "rounding of the thorax" was a decrease in stature, especially in the sitting height accompanied by senile curvature of the spine Nascher claimed that the erect posture caused the discs to become compressed with greater stress occuring anteriorly in the dorsal spine and resulting in a spread of the posterior borders This would account for the increased curvature in this region with the production of a kyphotic deformity

In a comprehensive study, Coventry, Ghormley and Kernohan

reviewed the histologic changes in the intervertebral discs occurring at various decades In the sixth decade, thinning of the disc was apparent in 3 of the 22 specimens Fibrillation of the ground substance and calcifications in the cartilaginous plate were common. The cartilage cells tended to lose their distinct outline and nuclei became pyknotic In the seventh decade, degeneration was extensive in 13 of the 27 cases Longitudinal bands of fibrous tissue and calcium plaques were evident In places, the cartilage was replaced by bone Tears were frequent with the annulus showing areas of necrosis and hyalinization. These changes were attributed to the excessive "wear and tear" to which the spinal column is inevitably exposed

The ribs accommodate themselves to the changed articular relations with the spine in back and the ossified costal cartilages in front by becoming flattened at the sides. These structural changes together with the lessened resiliency of the ribs themselves make for the typical senile chest which is longer anteriorly, foreshortened posteriorly, and flattened at the sides

Senescent changes in the synovial membranes, capsule ligaments and supporting tissues of the joints may be expected in the thoracic cage, as elsewhere in the body In upper costal respiration, the manner of articulation of the upper six ribs with the vertebrae results in an upward and forward movement of the anterior chest in inspiration, with relatively little lateral expansion of the ribs. On the other hand, when the ribs enclosing the lower half of the chest are raised in inspiration, there is a wide lateral flare With a diminution in mobility of the joints between the ribs and vertebrae posteriorly and the sternum anteriorly, the movements of the lower portion of the thorax would be especially impaired, thus handicapping the mechanics of respiration

Wasting and dehydration of the muscles of the chest wall have been described by Thewlis At times, there may be an actual proliferation of connective tissue fibers through the muscle bundles with resulting loss of elasticity The greatest atrophy appeared to take place in the intercostal muscles and diaphragm As a consequence of this muscle waste, the intercostal spaces and the supraclavicular fossae appear more prominent. These

changes in the musculature and ligamentous structures of the chest wall are not peculiar to aging alone but are frequently observed in severe malnutrition and certain wasting diseases.

In roentgenologic studies, Evans reported a loss of skeletal mineral content in the older subject accompanied at times by partial collapse of the vertebral bodies. This produced varying degrees of kyphotic deformity

The Lungs

The lungs, in their daily exchange of enormous amounts of air with the external environment, are more exposed to the adverse influences of such an environment and hence show the accumulation of pathologic insults in greater degree perhaps than any other organ of the body It is extremely doubtful if the pathologist in his necropsy material has an opportunity to observe age changes in the lungs *per se* Both Nascher and Rolleston indicated that the primary degeneration is one of atrophy resulting in a diminution in size and weight Reichinstein recorded an average change in the weight of the right lung from 570 grams in the age group 65 to 85 years to 438 grams between 85 to 90 years For the left lung, the corresponding figures are 430 grams to 350 grams It is frequently noted at the autopsy table that the lungs of elderly subjects do not exhibit the prompt collapse found in the young. Retractility is sluggish and deflation is incomplete Pathologists are inclined to accept a moderate degree of "alveolar emphysema" particularly of the peripheral portions and expanding edges as a normal finding in senescence In Laennec's classical description of the lungs of the aged, he stated, "The caliber of all their vessels seems diminished, the partitions of their air cells become thinner than natural, on which account, their substance rendered more rare, becomes less elastic, and thus yielding to the atmospheric pressure on opening of the body, they are found to occupy not more than one-third of the cavity of the pleura "

Senile deteriorations in the fibrous connective tissue making up the supporting framework of the lung are represented by a process of dehydration with a reduction in ground substance. In addition, the connective tissue stroma acting as a depository for the count-

less number of minute particles inhaled from the surrounding environment would tend to acquire an increased rigidity Atrophy of the epithelium has been described by Ashoff as involving a wasting of the columnar ciliated epithelium, degeneration of the bronchial glands and a loss of sensitivity of the mucous membrane As a result, the mucus formed in the bronchi and bronchioles would be thick and tenacious Changes in the lymphoid elements add to the over-all decline in flexibility and resiliency In this connection, both Saxton and Casarett have demonstrated that the lymphoid tissue in the lungs of rats increases with age to the extent that partial obstruction of the bronchial airway is produced favoring the development of chronic suppuration and emphysema Although Karsner mentions that senile pulmonary arteriosclerosis was frequent after the age of fifty and "practically constant after seventy years of age," the changes in the smaller blood vessels are difficult to divorce from alterations in the alveolar walls themselves

The increase in the amount and density of the fibrous connective tissue and lymphoid elements with their extension into the "root zone" and along the bronchial tree could seriously impair the normal elongation and retraction of these structures The deleterious effect of impaired bronchial movements on pulmonary ventilation is apparent In addition, Drinker and Warren have shown that the movements of the lung are extremely important in aiding lymph flow, and adequate drainage is interfered with when these movements are crippled

PHYSIOLOGIC CONSIDERATIONS

The measurement of lung volumes by numerous investigators indicate that there is little change up to the age of fifty Kaltreider, for example, found that the vital capacity is only slightly decreased from 40 to 50 years following which there is a more rapid decline This was confirmed by Arnett and W S Miller In addition, they noted that those individuals who continued to be active showed less fall than those retired from work The residual volume increases with age and constitutes a relatively larger fraction of the total lung capacity Kaltreider and associates and

Baldwin, Cournand and Richards found an increase in the ratio R V /T C from 20 per cent in the third decade of life to 31 per cent in the seventh decade This is in agreement with data quoted by Gilson and Oldham The maximum breathing capacity expressed as the largest volume of air voluntarily ventilated per minute also showed a significant decline with aging

In Darling's study on the index of intrapulmonary mixing as a measure of effective distribution of tidal air to the alveoli, he noted that three "normal" subjects over fifty years of age fell in a transition zone between the normal young adult and the clinically abnormal subjects He raised the question as to whether the lungs of elderly subjects could be considered entirely "normal" with respect to effective aeration of the pulmonary alveolar spaces. The anatomic dead space has been reported by Comroe as being larger for older men.

Although only a small group of apparently healthy subjects over the age of fifty were sampled (11 males and 15 females), Greifenstein and associates confirmed and extended many of the changes in respiratory function discussed above. An increase in the functional residual capacity with a mean of 41 per cent for the ratio R V /T C resulted in a smaller degree of alveolar dilution per breath The reduction of approximately 50 per cent in the maximum breathing capacity which was proportionately greater than the reduction in vital capacity suggested either a decrease in pulmonary elasticity, bronchial obstruction or compliance changes in the thorax. Eleven of the subjects showed abnormal intrapulmonary distribution of inspired gas which could be attributed to non-uniform obstructive processes, regional reduction in pulmonary elasticity coincident with aging or to changes in the dynamics of thoracic movements. Since no measurements were made of pressure-volume relationships in the lung-thorax system, there is no information concerning actual changes in pulmonary elasticity. The arterial oxygen saturation, pCO_2 and pH showed no significant differences from the values obtained in normal young adults These studies indicated that "definite changes may occur in the pattern of alveolar ventilation in older

subjects without producing disability and without being associated with any specific disease."

PATHOLOGIC CONSIDERATIONS

Chronic bronchitis is perhaps the most common ailment of the aged Sheldon reports an incidence of 40 per cent in his series of 477 subjects while Monroe documented 272 cases in his review Although chronic bronchitis implies an inflammatory process, pathologic descriptions have been somewhat varied In all probability, the basic defect *is an impairment in the self-cleansing* properties of the tracheobronchial tree With the diminished muscle tone, decreased sensitivity to stimuli and slowing of reflex activity so common in the aging process, the inability to produce an effective cough may result in an inadequate elimination of bronchial secretions in the older person and so predispose to chronic infection Deterioration in the normal ciliary activity may also favor the retention and accumulation of secretions

In many of the earlier accounts, emphysema accompanying senescence was thought due to an atrophy of the alveolar walls as a result of faulty nutrition The wasting of alveolar septae permitted the air cells to coalesce resulting in the so-called "small chest" emphysema in which the thoracic cage was more or less rigid and ventilation was carried on mainly by the diaphragm The preponderance of opinion regarding pathogenesis favors the one expressed by Kountz and Alexander who regarded senile emphysema as primarily the results of changes in the thoracic spine, particularly of the intervertebral discs Christie believes that these changes result in dorsal kyphosis with consequent rotation of the ribs so that the sternum is pushed forward and the chest becomes barrel-shaped The size of the thoracic cage is enlarged by virtue of this deformity and the lungs, in following the chest wall, become overdistended so that thinning and atrophy of the alveolar septae occur Figure 4 1 illustrates the typical kyphotic deformity and the barrel-shaped configuration of the chest in a 78-year-old patient admitted for the treatment of portal cirrhosis of the liver The lateral and postero-anterior roentgenograms of

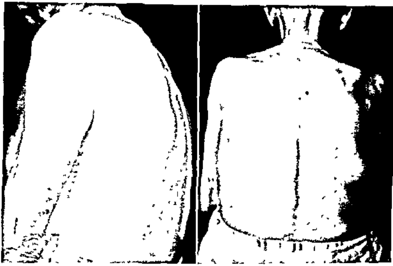


FIG 4 1 Typical kyphotic deformity and barrel-shaped configuration of the chest in a 78-year-old patient

the chest shown in Figure 4 2 reveals a marked "bowing" of the thoracic spine with wedging of the bodies of the 4th and 5th dorsal vertebrae Spur formation and lipping are prominent The increased AP diameter is readily apparent on the lateral view. Although there is an increased obliquity of the ribs with an increase in the interrib spaces, the diaphragm does not appear to be depressed and adequate motion may be demonstrated on fluoroscopy

Macklin and Macklin believe that "internal sclerotic" changes in all elements of the lung parenchyma due to the increased fibrosis limits the normal movements of the tracheobronchial tree including the lung root This fibrosis results in part from the aging process and from repetitive infections The central protions of the lung are particularly hampered in their movements and only the periphery is capable of expanding along with the thoracic cage The continuous stretching and overdistention of these peripheral alveoli finally causes breakdown of the alveolar walls The Macklins also raised the question of a diminished sensitivity in the receptors and afferent pathways initiating the act of expiration

FIG 4 2 Marked "bowing" of the thoracic spine with wedging of the bodies of the 4th and 5th dorsal vertebrae, increased AP diameter of the chest, spur formation and lipping of the vertebrae, increased obliquity of the ribs and an increase in the interrib spaces are illustrated

in maintaining the chest in the inspiratory state with a secondary deterioration in pulmonary elasticity Rappaport and Mayer contend that thoracic changes lead to senile emphysema in only a minority of the cases The essential lesion of emphysema at any age is the disappearance of the alveolar septae with progressive coalescence of the air spaces Functional disuse with loss of "breathing surface" is the main link in the pathogenesis of senile emphysema "The natural process of involution in the senile lung results in a lung defect which is identical with the developmental and acquired defects of hypertrophic emphysema " The "involutional lung defect" develops into emphysematous changes upon the intervention of the mechanical forces inherent in the labored respiration accompanying dyspnea

I share the general clinical impression that senile emphysema is for the most part of little serious significance In contrast to obstructive emphysema, measurements of pulmonary function are little impaired, nor is the arterial oxygen saturation of the

blood significantly altered On the other hand, Hansen-Pruss and Charlton state that the degree of pulmonary insufficiency is not proportional to the anatomic changes and believe that ventilatory function may deteriorate to a considerable extent. Most of their subjects had evidence of bronchial obstruction and probably represented combinations of hypertrophic and senile emphysema Franklin, in a recent study on the clinical value of tracings of forced expiration, concurs that many older patients exhibiting thoracic deformities associated with emphysema do not have clinically significant pulmonary disease Although the vital capacity is reduced, the "expirogram" is normal and no change occurs following the administration of broncholidator drugs Although the chest deformity may limit the motion of the thoracic cage, it interferes little with respiration Since the diaphragm is rarely affected, it retains its capacity for excursion In fact, breathing in the aged may be largely abdominal in type and unless there is marked loss of abdominal tone, interference with respiratory function rarely compares to that of obstructive emphysema It may limit physical exertion or be an aggravating factor in other disease states. In this connection, heart disease with congestive failure frequently overshadows the presence of senile emphysema.

The clinical manifestations of these other diseases frequently associated with senile emphysema have occupied the attention of the physician leading to widespread neglect in the treatment of this type of emphysema Since obstructive factors are minimal or lacking, bronchodilator agents are usually ineffective. The vigorous treatment of chronic indolent infections of the bronchial tree with chemotherapeutic and expectorant drugs will be discussed more fully in Chapter 8 The prompt use of the newer antibiotic agents in acute respiratory infections prevents further deterioration which accompanies the flare-up of a chronic infection Although the cough reflex is perhaps the most important mechanism of eliminating retained secretions from the respiratory passageways, the ineffectual paroxysms of dry, hacking cough caused by inflammation of the bronchial mucosa may seriously endanger the life of the elderly debilitated patient. Of special importance for long term care, the recognition of the necessity for

maintaining body tone and physical fitness by a program of exercise designed to improve the mechanics of respiration has assumed a major role in our therapeutic armamentarium. This has been more fully discussed in Chapter 3. If "disuse atrophy" plays any part in the pathogenesis of senile emphysema as has been suggested by Rappaport and Mayer, graded respiratory exercises adapted to the exercise tolerance of the patient will result in clinical improvement and arrest further deteriorations.

In summary, the characteristic features which distinguish senile from hypertrophic emphysema are the absence of bronchial obstruction, a normal or slightly decreased total lung volume and a slight reduction in compliance consistent with the loss of elasticity in other tissues of the body as a result of the aging process. The primary defect appears to be a structural alteration in the thoracic cage due to degeneration of the intervertebral cartilaginous discs producing a postural deformity characterized by kyphosis and an increased AP diameter. Respiratory insufficiency is seldom severe unless complicated by heart failure, superimposition of obstructive emphysema, or associated obesity and hypotonicity of the abdominal musculature (Kerr). Greifenstein and his co-workers while inclined to disagree with the theory of kyphotic deformity conclude that "until there is further opportunity for correlating clinical, physiologic, radiologic and pathologic studies in patients of this type, there seems to be little to be gained by using designations such as 'senile', 'postural' emphysema to characterize pulmonary changes in this group. Lungs 'normal for their age' probably do not have the same reserve as those of young adults."

A selective bibliography is given on page 234

Chapter 5

CORTICOTROPIN AND THE ADRENOCORTICOSTEROIDS IN THE TREATMENT OF PULMONARY EMPHYSEMA

HYLAN A BICKERMAN, M D

Introduction

An extensive literature on the effects of corticotropin and the adrenal steroids in various disease states has accumulated in the past six years since Hench and his co-workers reported their initial studies on the effects of these hormones in patients with rheumatoid arthritis Shortly thereafter, it became apparent that the administration of these substances to patients with many different diseases resulted in a remarkable improvement in their clinical pictures The wide variety of disease entities affected, both in terms of etiology and clinical manifestations, provided few clues as to the possible pharmacologic mechanisms involved since a common denominator to explain the obvious benefits observed appeared to be lacking

The early reports of Bordley, Randolph and Rose indicated that dramatic relief of the symptoms of asthma was obtained with *cortisone and ACTH* *Other allergic states such as hay fever,* vasomotor rhinitis, and allergic dermatitis were similarly benefitted Subsequent studies by Thorn, Baldwin, Schwartz, and others confirmed that partial or complete relief of symptoms could be expected in over 80 per cent of patients with bronchial asthma treated with these hormones Barach and I reported comparable findings after 200 courses of corticosteroid therapy in 100 patients with asthma as well as in the majority of approxi-

mately 100 courses administered to 50 cases of pulmonary emphysema. In addition significant benefit was obtained in 2 cases of pulmonary fibrosis. The effects of corticotropin and the corticosteroids on various diseases of the pulmonary system have been reported. Variable results have been obtained in patients with pulmonary granulomas due to sarcoid or the pulmonary manifestations of the diffuse collagen disorders such as scleroderma, disseminated lupus erythematosis, and periarteritis nodosa. In the early stages of beryllium granulomatosis, however, hormonal therapy has resulted in the arrest of, and in some instances, apparent resolution of the pathologic process.

Until recently only fragmentary statements are found in the literature concerning the effect of these hormones in the treatment of chronic pulmonary emphysema. Yet, the increasing importance of this progressively disabling disease is reflected by an incidence among populations of industrialized areas far greater than has heretofore been recognized. Since pulmonary emphysema is frequently associated with other pathologic states, much of the information is buried in studies on chronic bronchial asthma, silicosis, and pulmonary fibrosis of unknown etiology. Hansen-Pruss, in reviewing the literature, found marked variations of between 1 per cent to 65 per cent as the reported incidence of pulmonary emphysema complicating bronchial asthma. In his own series, he estimated that approximately 35 per cent of the patients with chronic asthma had anatomic emphysema.

Irrespective of the underlying mechanism in the causation of chronic pulmonary emphysema, most authorities agree that one of the major defects in the physiopathology of this disease is the presence of bronchial or bronchiolar obstruction with disturbances in air flow. Ventilation studies reveal serious ventilatory defects in the majority of patients. An increased resting ventilation, a decreased maximal breathing capacity, a markedly diminished ventilatory reserve, and an elevation of the index of intrapulmonary mixing are noted. "Essentially similar findings were recorded in patients with chronic bronchial asthma" (Segal). Unlike asthma, however, there is always some irreversible residual defect even with the most vigorous therapy. Before proceeding to

a discussion of the clinical evaluation of hormone therapy in pulmonary emphysema, the physiologic and pharmacologic activities of these substances will be reviewed briefly. For more detailed information, the reader is referred to the comprehensive reports by Thorn, Ingle and Kinsell.

Pharmacologic Aspects

The secretory activity and histologic appearance of the adrenal cortex are regulated for the most part by the adrenocorticotropic hormone of the anterior pituitary. In preserving many of the homeostatic mechanisms upon which life depends, the anterior pituitary adjusts its output of corticotropin to meet the physiologic requirements of the organism for cortical hormones. This response of the anterior pituitary is regulated in part by (1) the level of circulating adrenal hormones, or metabolites thereof, (2) neurohumoral mechanisms originating in the hypothalamus, and (3) stimulation by epinephrine especially in situations of acute stress which activate the sympathetic nervous system. Ingle has demonstrated that the anterior pituitary is sensitive to the "needs" of the body for adrenal cortical hormones and releases increased amounts of corticotropin during stress so that increased secretory activity and hyperplasia of the adrenal cortex results. He has shown experimentally that in the presence of an excess of exogenous cortical hormone, the release of ACTH by the anterior pituitary is suppressed so that atrophy of the adrenal cortices takes place.

Selye has postulated that the hormones of the adrenal cortex are major etiologic factors in many conditions which he has called "diseases of adaptation." An intact anterior pituitary-adrenal cortical system is essential for the manifestations of certain diseases and this is one of the major points supporting Selye's theory that an overproduction or imbalance of these hormones causes disease.

The adrenocortical hormone has been shown recently to consist chiefly of two steroids, 17-hydroxycorticosterone or hydrocortisone and corticosterone with smaller amounts of a third steroid, aldosterone. Although the physiologic effects of cortisone are

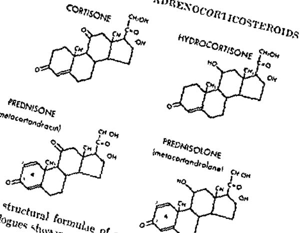


FIG 5 1 The structural formulae of cortisone and hydrocortisone together with their Δ' analogues showing their double bond between carbons 1 and 2

similar to hydrocortisone, it does not appear to be a significant component of natural adrenocortical hormone in man The structural formulae of cortisone and hydrocortisone together with the new synthetic steroids prednisone and prednisolone are presented in Figure 5 1 Although most of the major metabolic and therapeutic actions of these steroids are similar, certain important differences exist which are essential to their proper evaluation in therapy Thorn and his co-workers in assessing these differences state that "the anti-inflammatory activity of adrenal steroids parallels in general their carbohydrate-regulating and pituitary-inhibiting activity A broader spectrum of therapeutic usefulness is more likely to be associated with the enhancement of the ratio of organic metabolic-regulating activity to inorganic or salt-retaining potency" The relative potencies of these steroids in man with hydrocortisone as a standard is shown in Table 5 1 The netabolic activity of hydrocortisone is approximately twice that f cortisone, and, in addition appears to be vastly superior to ortisone on local administration such as intra-articular injection nd application to the eye and skin The introduction of a double ond between carbons 1 and 2 of cortisone or hydrocortisone to m the Δ' compounds enhances the anti-inflammatory potency hough physiologically less active than aldosterone or the fluoro

TABLE 5 1

	Carbohydrate Activity	Salt Retention	Sugar/Salt Ratio
Hydrocortisone	1	1	1
Prednisone	4	1	4 0
Fluorohydrocortisone	20	50+	0 4
Aldosterone	<1	50+	0 02

From Thorn, G W et al Ann Int Med 43 979, 1955

derivatives, prednisone exhibits a higher therapeutic index for those diseases in which an anti-inflammatory or anti-allergic response is desired and in which excessive sodium retention imposes a limiting factor

The adrenocorticotropic hormone of the anterior pituitary has not as yet been isolated in pure form, but it is a polypeptide consisting of between 7 to 9 amino acids. The physiologic and biologic effects elicited by corticotropin are qualitatively similar to those mediated by the adrenal steroids. It differs from the steroids in that it often produces pigmentation of the skin due to an increased melanin content The steroids are effective on oral administration and are rapidly absorbed from the gastro-intestinal tract whereas corticotropin must be given parenterally.

A brief description of some of the metabolic effects of these steroids and the alterations they produce in various organs and tissues of the body is pertinent to their proper evaluation in therapy especially since the desirable effects must be weighed against adverse reactions These physiologic effects include

(1) The stimulation of gluconeogenesis from protein and an inhibitory action upon carbohydrate utilization reflecting the diabetogenic characteristic of these hormones.

(2) Increased protein catabolism with an augmented excretion of uric acid resulting in a negative nitrogen balance.

(3) Sodium and chloride retention with increased potassium excretion There is a shift in fluids from the intracellular to the extracellular compartment

(4) Thinning of the skin, formation of striae, rounding of facies

due to increased fat deposition, and presence of acne and hirsutism

(5) Muscle weakness from potassium depletion, osteoporosis with pathologic fractures due to a negative nitrogen, calcium and phosphorus balance

(6) Retardation of wound healing with delay in fibroplasia, increased vascular fragility, eosinopenia, lympholysis, reticulocytosis, and possible interference with the phagocytic activity of the reticuloendothelial system

(7) Increase in gastric hydrochloric acid and pepsin secretion

(8) Euphoria, restlessness, fluctuating mood with occasional psychotic reactions. Brain excitability is increased with a lowering of the electroshock threshold and presence of paresthesias

(9) Menstrual irregularities; decreased iodine uptake by the thyroid; and occasional disturbances in growth

The major therapeutic effects of these hormones in the management of pulmonary emphysema are related to a suppression of the processes of inflammation and an alteration of the allergic response Systemic manifestations of infection such as fever and toxemia are suppressed in addition to the decrease in exudate, phagocytosis and vascular permeability Although dramatic effects are achieved with these agents in diseases of allergic origin, the precise mechanism of action is unknown and the basic allergic state is unaltered These hormones do not inhibit the union of antibody and antigen and the immediate skin reaction to test allergins remains unchanged.

Another important effect of these steroids appears to be an increase in the resistance of the organism to withstand certain, although not all, forms of stress such as starvation, extreme physical exertion etc Whether this increased tolerance to stress parallels the metabolic effects of these agents or involves other unrelated activities has not been established

Since the mechanisms and site of action of the steroid hormones have not been elucidated, it has been speculated that their therapeutic activity involves not only the many known physiologic properties of these hormones, but also various thus far undis-

covered effects on the bio-chemical processes of organs, tissues, and cells of both the normal and the diseased organism. It is now clinically apparent that corticotropin and the adrenal steroids are capable of suppressing the local and systemic response of the organism to a wide variety of noxious agents Similarities between the effect of these hormones on the hypersensitive state and inflammatory response of connective tissue suggest that the common denominator may be a modification of the reactivity of mesenchymal tissue at the cellular level (Thorn)

The various *preparations of corticotropin and the adrenal* steroids available for clinical use and their commercial packaging has been listed by J C Beck In the therapy of chronic respiratory disease in our clinic, we have employed the following preparations: corticotropin-H P (short acting) and H P gel (long acting), cortisone acetate-aqueous suspension for intramuscular use and oral tablets, and hydrocortisone in oral tablet form During the past year, extensive clinical use has been made of prednisone and prednisolone in a tablet form for oral ingestion. More recently, we have received an aqueous suspension of prednisolone (Meticortelone) acetate containing 25 mg per cc for intramuscular administration Preliminary studies on this preparation are in progress

The dosage schedule employed with these preparations will be discussed under clinical management. It is important to emphasize at this point that the quantities of these hormones commonly administered in the treatment of various disease states far exceeds the amount normally secreted by the adrenal cortex Replacement therapy in Addison's disease and after surgical removal of the adrenal cortices has been accomplished with 15 to 30 mg of cortisone daily representing the physiologic dosage level To be pharmacologically effective in suppressing the manifestations of other diseases, overdosage is usually necessary, and thus, it is inevitable that *some alterations in the normal metabolic processes* will accompany such therapy Many of the so-called adverse reactions to be discussed later in this chapter are a concomitant of effective therapy. Fortunately, the majority of these changes

can be prevented or minimized by certain specific measures and in many instances tend to disappear when therapy is discontinued

Clinical Management

Although the dramatic effects of corticotropin and the adrenal steroids in the treatment of intractable bronchial asthma and status asthma scarcely needs further documentation, there is still some controversy regarding the effectiveness of these hormones in chronic pulmonary emphysema The high incidence of chronic bronchial asthma in patients with pulmonary emphysema and the presence of chronic pulmonary infection in over 50 per cent of such patients at necropsy (Monroe) are further proof that obstructive factors play an important role in the pathogenesis and course of pulmonary emphysema It is the experience of many clinicians that the administration of bronchodilator agents frequently produces partial relief of the dyspnea associated with pulmonary emphysema even though there may be no apparent clinical evidence of bronchospasm or resistance to air-flow on examination Ventilatory function studies indicate that the relief of obstruction permits better distribution and mixing of inspired gas with improvement in the efficiency of ventilation Lukas has presented evidence that ACTH and cortisone produce changes in pulmonary function qualitatively similar to those achieved with conventional bronchodilators The temporary improvement in these patients has been attributed by Ferris to a reduction in bronchiolar resistance to air flow since the timed vital capacity and the maximum breathing capacity showed far more change than the lung volume compartments Fyles, moreover, indicated that a more complete and continuous relief of bronchospasm is afforded by these hormones as compared with epinephrine and aminophylline The change in clinical management resulting from the introduction of prednisone will be referred to below

Indications

In the sense that the adrenal steroids produce an alteration in the body's reaction to disease rather than a cure of the disease

process itself, these agents provide only symptomatic therapy at a "magnificent level" which, at times, may be life-saving.

The *indications for the use of corticotropin and the adrenal steroids in chronic pulmonary emphysema are in one respect similar to those in intractable bronchial asthma. Not infrequently, the patient with pulmonary emphysema will experience an acute episode of pulmonary insufficiency precipitated by severe bronchospasm This is often the result of an acute respiratory infection, exposure to inhaled irritants or allergins to which the patient is sensitive, or cardiac insufficiency In many instances, the treatment of this acute state resembles that of status asthma When the reversal of these functional disturbances cannot be induced by the vigorous application of conventional measures such as bronchodilator agents, oxygen and helium-oxygen therapy, antibiotics, and pressure breathing, the use of the corticosteroids becomes mandatory In practice, prednisone has now been almost completely substituted for cortisone. In addition to tiding the patient over this critical period, their secondary value, as emphasized by Segal, of increasing the patient's appetite and sense of well-being aids in the restoration of normal hydration and nutrition By relieving the dyspnea and hypoxia caused by intractable bronchospasm, convalescence is shortened and measures designed to improve ventilatory mechanics such as diaphragmatic breathing and postural exercises may be more promptly and effectively instituted

Contraindications

Many investigators have cautioned against the use of the older steroids in pulmonary emphysema with associated pulmonary hypertension or cor pulmonale (Rose, Beck, Spain) Galdston noted deterioration in pulmonary function in one patient with long standing pulmonary emphysema, and Lukas found further depression of the gas exchange in a patient with cor pulmonale which was attributed to the development of edema of the alveolar membrane. The danger of markedly accentuating the existing respiratory and circulatory defects by salt and water retention had been cited as one of the major contraindications to the use of

steroid therapy This situation no longer exists with prednisone in the usual therapeutic dosage, but was true of cortisone and ACTH. We have observed patients in cor pulmonale whose cardiac status has improved when the hypoxia and marked dyspnea accompanying severe bronchospasm has been relieved by steroid therapy

In the light of our present experience, the presence of diabetes mellitus, peptic ulcer and active pulmonary tuberculosis would serve as serious deterents to initiating therapy with these hormones No difficulty has been encountered in patients with mild to moderate hypertension with prednisone, but osteoporosis with spontaneous fractures represents a special problem in view of the age group in which the majority of the patients fall and the high incidence of skeletal thoracic deformity Before treatment is contemplated, it is essential that a clinical appraisal be made for the detection of diabetes or peptic ulcer including a chest film to evaluate the presence of pulmonary tuberculosis

Methods of Therapy

Therapeutic management with these agents must be individualized for each patient since they are nonspecific and the optimum dosage is usually a matter of trial and error based on the clinical acumen of the physician In general, the amounts required are related to the severity of the disease process rather than to body weight or age The clinical responses of the patient may be highly variable requiring frequent changes in schedule so as to establish the maximal therapeutic benefit with minimal adverse reactions

1. CORTICOTROPIN

In the past, corticotropin was initially administered in dosages of 25 mg intramuscularly at 6-hr intervals When highly purified gel preparations became available, 80 mg were given once daily until relief became clinically apparent, usually by the second or third day The dosage was then gradually reduced in stepwise fashion to 60 mg daily for two days and then 40 mg In our series of 130 courses of ACTH, the total dose ranged between 240 mg and 960 mg given over a period of 3 to 12 days Moderate to

excellent remissions manifested by a decrease in bronchospasm, reduction in cough and expectoration and an increase in exercise tolerance were obtained in 85 per cent of the patients, the 15 per cent who experienced little or no relief were classified as failures For the most part, the duration of remission following cessation of therapy was disappointingly short, averaging 14 days Many of the patients relapsed within a few days and only 3 reported improvement which persisted over two months.

On a few occasions when a more rapid effect was considered desirable, particularly in the critically ill patient, corticotropin was administered intravenously in doses of 20 mg. dissolved in 1,000 cc of 5 per cent dextrose in distilled water with 40 mEq of potassium chloride added This was administered slowly over a 10-hr period for the first day or two at which time 60 mg daily of the long acting gel preparation was substituted intramuscularly Since the intensity of adrenal cortical stimulation is a direct function of the maintenance of a high level of circulating ACTH, the effects of 20 mg. of corticotropin administered in a slow infusion are comparable to 100 to 150 mg. of ACTH given by the intramuscular route (Thorn).

2 CORTISONE AND HYDROCORTISONE

A total of 88 courses (46 cortisone, 42 hydrocortisone) of adrenal corticosteroid have been administered in our study to 56 patients with advanced pulmonary emphysema. In this group of patients, short intensive courses of steroid therapy were given with initial peak doses of 200 to 300 mg daily in 4 divided doses for rapid, effective relief followed by a quick tapering off over a period of 10 to 14 days During the past 2 years, 40 to 60 mg. of corticotropin gel has been administered once daily for the last 3 to 4 days of steroid therapy The dose of hydrocortisone averaged between 60 to 70 per cent of that employed with cortisone Adjuvant therapy will be discussed in the section dealing with adverse reactions The clinical response of the patients treated with cortisone and hydrocortisone was similar to that of the corticotropin treated group

Approximately 100 or more courses of these steroids have been administered in the past year in our clinic. We have been unable to detect any significant differences in either dosage requirement, therapeutic effectiveness or toxic manifestations between prednisone and prednisolone, although a few patients expressed a preference for one over the other. These analogues of cortisone are given in 4 divided doses, at mealtimes and between 11 and 12 p.m. generally with milk. In determining the most suitable ...losage, severe bronchospasm is considered an indication for ...osages of 60 to 80 mg per day for the first day or two, followed ...y a decrease of 10 to 20 mg each two or three days thereafter ...pending upon the response of the patient. At the end of 7 to ... days, an approximate maintenance dose of 10 to 25 mg per ... is instituted which frequently requires temporary revision ...ed on the clinical state of the patient. In patients with mod-...e bronchospasm, an initial dose of 40 to 50 mg of prednisone ...lted in rapid improvement.

... with corticotropin and the adrenal hormones, marked to ...rate relief of obstructive dyspnea occurred in approximately ...r cent of the patients treated. However, a more rapid re-... was especially evident in those cases previously treated ...ortisone or ACTH. The mean onset of improvement as ...ined by a diminution in dyspnea and wheezing, occurred ...rs after the start of therapy. Thirty-two per cent of the ... noted some relief within 24 hours while only 8 per cent ... 72 hours or more of drug administration before noticing ...fit. This is illustrated graphically in Figure 5 2. A sum-...he clinical effect of these hormones is listed in Table 5 2.

Effect on Pulmonary Function

...us authors have published reports of the effect of ...in and adrenal steroid therapy on the pulmonary func-...tients with pulmonary emphysema (Lukas, Ferris, ..., Kennedy, Brown, Bickerman and Barach). It has ...strated that bronchospasm and the allergic production

of obstructive mucus, which constitute the main functional defects in bronchial asthma, are reversible when treated with adequate amounts of the adrenal hormones "The more complete the removal of symptoms with such therapy, the more complete is

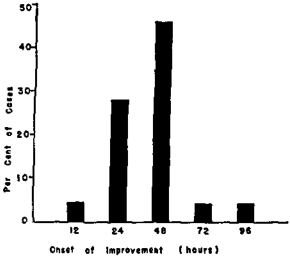


FIG 5 2 Time relationships showing the onset of improvement of dyspnea In the majority of 50 patients with pulmonary emphysema relief became apparent within 48 hr after the start of prednisone therapy (Bickerman, H A, Beck, G J, and Barach, A L J Chronic Dis., 2: 247, 1955)

TABLE 5 2
Clinical effect of corticotropin and steroid therapy in patients with pulmonary emphysema

Therapeutic Agent	Mean Onset of Improvement	Clinical Improvement* (Per Cent of Courses)		
		Marked	*Moderate*	*None*
	hours			
Corticotropin-H P gel	56	26	59	15
Cortisone	96	39	39	22
Hydrocortisone	60	40	42	18
Prednisone	44	48	42	10

* Objective criteria for improvement include diminished bronchospasm on physical examination and increased exercise tolerance

the return to normal pulmonary function." In this respect, ventilatory function tests reveal little change, either qualitatively or quantitatively, from the relief obtained with other effective bronchodilator agents such as epinephrine or aminophylline Similar results were obtained by Kennedy in patients with pneumoconiosis and pulmonary emphysema in whom cortisone therapy failed to enhance the improvement in the maximum ventilatory capacity produced by aerosol epinephrine The structural defect in pulmonary emphysema places a limiting factor on the extent to which ventilatory function can be improved Nevertheless, tests of pulmonary function will often determine the amount of bronchial and bronchiolar obstruction present and thus provide a rough gauge as to the possible effectiveness of steroid therapy

The variable response to ACTH and cortisone on pulmonary function studies, in patients with pulmonary emphysema has been noted by West and Galdston Five of the nine patients studied by Brown and associates showed a significant improvement

FIG 5 3 The vital capacity of 15 patients with pulmonary emphysema The more striking increases in vital capacity after prednisone occurred in those patients who exhibited clinical evidence of bronchospasm and had not been previously maintained on cortisone (Bickerman, H A, Beck, G J, and Barach, A L J Chronic Dis, 2: 247, 1955)

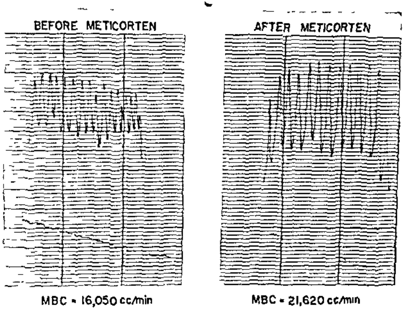


FIG 5 4 A significant increase of 34 per cent in the maximum breathing capacity was observed during prednisone (Meticorten) therapy in a patient with severe ventilatory insufficiency due to pulmonary emphysema (Bickerman, H A, Beck, G J, and Barach, A L; J Chronic Dis, 2, 247, 1955)

in ventilatory function after intravenous ACTH They concluded that patients with long standing emphysema and fibrosis with a restrictive type of ventilatory insufficiency obtain little or no benefit from ACTH, but patients with the obstructive type of ventilatory defect may be greatly improved. Ventilatory function studies on 15 patients before and during prednisone therapy reported by Bickerman, Beck and Barach showed a mean increase of 32 per cent in the vital capacity and 21 per cent in the maximum breathing capacity It was of interest that the first five subjects presented in Figure 5 3 who showed no significant change had extensive pulmonary fibrosis with little or no bronchospasm Spirographic tracings of the maximum breathing capacity

of a patient with severe obstructive emphysema are illustrated in Figure 5 4 The improvement in ventilatory function produced by prednisone probably resulted in part from a reduction in mucosal edema, inflammatory or allergic, of the tracheobronchial airway as well as relief of bronchospastic dyspnea In addition, an improved oxygen diffusion seemed to take place in those patients with pulmonary fibrosis in whom little or no bronchospasm was detected clinically This was strikingly manifested in four of our cases, and was indirectly substantiated by the decrease in the resting ventilation during prednisone therapy and more especially by the reduction in the air-oxygen ventilatory difference when 100 per cent oxygen was substituted for room air

Duration of Therapy

The duration of a course of steroid therapy must be as highly individualized as the dosage schedule Corticotropin and the adrenal steroids have been found exceedingly useful in tiding the seriously ill patient over an acute episode of bronchospasm which is refractory to other forms of remissive therapy These acute episodes in the course of pulmonary emphysema commonly arise as a sequelae of an upper respiratory infection or exposure to an increased concentration of inhalant allergins such as dust or pollens Short, intensive courses with prednisone are now employed in preference to ACTH or cortisone for the most part These short courses of prednisone range between 10 to 14 days

Just as in chronic intractable asthma, the bronchospasm of some patients with obstructive emphysema continues to remain refractory to the ordinary measures designed to relieve bronchospasm Burrage and associates have expressed the opinion that maintenance therapy with the older steroids appears justified in selected patients with intractable asthma of unknown etiology who cease to respond to any conventional form of therapy Similar justification exists for the use of maintenance therapy in this form of emphysema, especially since salt and water retention are minimized by the use of prednisone By so doing, many of these

patients have been restored to partial activity. Marked improvement in morale accompanies their "escape" from social and economic invalidism From a practical point of view, the aim has been to afford some relief of bronchospasm since a complete remission is unobtainable Furthermore, it is desirable to reduce the need for larger doses of prednisone by employing conventional bronchodilator therapy in conjunction with prednisone. Despite the smaller dosage of hormone required to accomplish this, varying degrees of hyperadrenalism inevitably result.

The majority of the patients in our series have been maintained on the oral form of the adrenal steroids. Formerly, 75 to 125 mg of cortisone daily were employed When hydrocortisone became available, the average dosage level ranged between 40 to 80 mg. per day, but in the past year, prednisone or prednisolone has been substituted for the other steroids in almost all of these patients at an approximate level of 10 to 20 mg. daily in divided doses Rose and Kinsell have pointed out that since the adrenal steroids may produce marked but transient atrophy of the adrenal cortex by suppression of endogenous corticotropin secretion, it would be safer from a theoretical standpoint to administer alternating courses of steroid and corticotropin. This may be an important consideration since patients on the relatively short intensive schedule generally do not develop untoward symptoms whereas the incidence of adverse reactions increases with maintenance. Studies by Engleman and Fredell have shown that suppression of adrenocortical function may be reversed by the administration of corticotropin even though the maintenance dose of cortisone is continued. Some of our patients on maintenance prednisone therapy receive 60 mg of corticotropin gel weekly or semimonthly. However, the advisability of corticotropin supplementation is still debatable

Adverse Reactions

Since the therapeutic effectiveness of these hormones requires dosages in excess of the normal daily endogenous secretion, the majority of the adverse side effects are a result of hypercorticism

As already noted, the incidence of these reactions appears to bear a direct relationship to the quantity of steroid administered and the duration of therapy. In a report by Bickerman and Barach, a significant decrease in the number of adverse reactions was observed when hydrocortisone at dosage levels 50 to 60 per cent that of cortisone was administered to patients with bronchial asthma and obstructive emphysema. This was in confirmation of the statement by Thorn that "the increased potency of hydrocortone without a proportionate increase in toxicity may be an important factor in making this steroid the hormone of choice in the therapy of diseases responding to corticotropin or the adrenal steroids." The demonstration that the newer analogues of cortisone such as prednisone and prednisolone possess greater therapeutic potency without salt and water retention at smaller dose levels raises the possibility that further alterations in the structural formulae of these steroids may one day produce the "hormone of choice."

The more common evidences of hyperadrenalism encountered in the author's series included rounding or "mooning" of the facies, abnormal fat distribution about the pelvis, abdomen and shoulder girdle, hirsutism and acne. The increase in girth may be accompanied by striae. Figure 5.5 A illustrates the marked deposition of fat in the axillary folds and about the shoulder girdle in a patient with intractable bronchial asthma who had been maintained on cortisone and hydrocortisone for over 2 years. A prominent "buffalo hump," not visible in this photograph was also present. igure 5.5 B presents the same patient after nine months of ednisone therapy at a maintenance level of approximately 15 g daily. With the substitution of prednisone for hydrocortisone, ict adherence to a high protein, low caloric diet, and the use dextro-amphetamine this patient lost a total of 60 lb. with ost complete disappearance of the evidences of abnormal fat ribution. Alterations and occasional suppression of the menl cycle have been noted. These reactions, for the most part, of minor importance and did not contraindicate continued pı

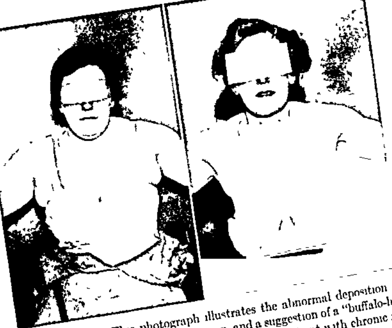


FIG 5 5 (Left) This photograph illustrates the abnormal deposition of fat in the axillary folds, supraclavicular region, and a suggestion of a "buffalo-hump" which occurred on prolonged cortisone therapy in a patient with chronic intractable asthma and pulmonary emphysema

(Right) The disappearance of these abnormal fat depots occurred 9 mo. after the substitution of prednisone for cortisone. It is of interest that during this time the patient adhered to a high protein, low caloric diet which she had difficulty following while on cortisone therapy

Significant salt and water retention is a serious consideration especially in patients with latent or overt cor pulmonale or cardiac insufficiency due to other causes Further impairment of the circulation resulting from the hypervolemia induced by hormone therapy (ACTH and cortisone) may precipitate acute congestive failure. Thirteen patients, in the author's original series of 62, had evidence of fluid retention with edema. Two of these with advanced pulmonary emphysema who had failed to restrict their salt intake while on corticotropin therapy developed acute pulmonary congestion. With proper attention towards improving the cardiac status of the patient, a low sodium diet, and the use of digitalis and the mercurial diuretics when necessary, fluid reten-

tion was at times controlled In many instances, however, edema was present and adequate regulation of salt impossible in an office practice Excessive weakness due to potassium depletion occasioned by these hormones, accentuated by the use of mercurial diuretics can be ameliorated by potassium chloride supplementation at a dose of 3 to 4 gm daily The lack of sodium and fluid retention or significant potassium depletion encountered with prednisone at the customary therapeutic dosage level appears to have provided a solution to this problem

Altered mental states ranging from mild euphoria to severe depression or frank psychotic behaviour have been reported Increased irritability with insomnia and at times paresthesias have been controlled by adjusting the dose of steroid and administering appropriate sedatives Serious aberrations of affect require the cessation of therapy Since this type of reaction is more prone to occur in patients with a previous history of mental disturbance, careful selection of patients will serve to minimize this complication

The more serious side effects of therapy with corticotropin and the adrenal steroids include the development and masking of intercurrent infection, reactivation of peptic ulcer and accentuation of generalized osteoporosis complicated by pathologic fractures These have been extensively reviewed by Rose, Burrage, Jefferies, Ragan, Irwin, and Bollet among others Similar effects may occur with prednisone

In a chronic debilitating disease such as pulmonary emphysema the reactivation and spread of a latent infection while on prolonged steroid therapy is a distinct possibility In a high percentage of the patients who did not obtain adequate relief from hormone therapy, in our series, the failure was attributed to the exacerbation of a sinobronchial infection The administration of an appropriate antibiotic as determined by sensitivity tests using the disc method is usually effective in maintaining improvement from continued hormone therapy Both Segal and Rose have suggested the concomitant administration of broad spectrum antibiotics in all patients on a prolonged course of steroids However this has not appeared necessary in many instances, when the gross character of the sputum is inspected at frequent intervals

The evidence, quoted by Johnson, that the steroids have adversely effected tuberculosis both in experimental animals and man was strikingly apparent in one of our patients who took cortisone over a 3-mo period against advice and developed widespread bilateral pulmonary tuberculosis Previous chest films during the preceding five years had been negative for tuberculosis Evans has listed the pulmonary complications of hormone therapy and emphasizes that these complications are frequently overlooked because of the masking of symptoms by the suppression of the normal inflammatory responses Frequent chest roentgenograms and the smear and culture of sputum when infection is suspected may aid in an early diagnosis

In view of the number of reports concerning the reactivation of peptic ulcer with bleeding or perforation, the use of these hormones in the presence of a past history of an ulcer is obviously hazardous. Because of the high incidence of dyspeptic complaints consisting of abdominal distention, eructation, flatulence and occasionally epigastric pain, the steroids are routinely administered with milk after meals, followed by an antacid preparation one to two hours after eating and on retiring. In selected cases, anticholinergic agents have been added to the treatment schedule There have been two instances of bleeding peptic ulcer in patients who had no history of ulcer in our entire series, first suspected when melena became apparent The rapid development of frank hemorrhage in a patient with a known ulcer after only 4 days of prednisone therapy may or may not have been due to the drug

One of the most serious and perhaps irreversible side effects of prolonged steroid therapy is the development of osteoporosis with compression fractures of the vertebral bodies Although Rose believes that dietary management with a high protein, calcium and vitamin D intake together with testosterone may be helpful in preventing or aiding repair of the osteoporosis, considerable controversy exists regarding the benefit of calcium salts or testosterone-estrogen combinations The x-ray of a 65-year-old patient with advanced pulmonary emphysema is presented in Figure 5 6 A In addition to generalized osteoporosis, a compression fracture of the 11th dorsal vertebra was noted in December 1953 after

FIG 5 6 (Top) A compression fracture of the 11th dorsal vertebra was noted in December 1953 after approximately 1 year of hydrocortisone therapy in a patient with advanced pulmonary emphysema

(Bottom) X-rays of the dorsal spine in August 1955 after 6 mo of prolonged prednisone therapy revealed wedging and compression of the 7th dorsal vertebra marked osteoporosis and further collapse of the 11th dorsal and bony bridging

approximately 1 year of intermittent therapy with hydrocortisone In August 1955 while on maintenance prednisone therapy averaging 15 to 20 mg daily, he experienced an acute episode of severe midback pain radiating to the lower anterior chest Roentgenograms revealed wedging and compression of the 7th dorsal verte-

TABLE 5 3

Incidence of adverse side reactions in patients with pulmonary emphysema treated with corticotropin and the adrenal steroids

Adverse Reactions	Corticotropin (% of 130 Courses)	Cortisone & Hydrocortisone (% of 88 Courses)	Prednisone (% of 100 Courses)
Mild hyperadrenalism (mooning of facies, hirsutism, acne and abdominal fat deposition)	6.7	7 2	6 0
Significant fluid retention	8 0	6 0	0
Disturbed mental state	1.5	2 3	2 0
"Anaphylactoid" reaction	2 4	0	0
Epigastric distress	1 6	5 6	12 0
Activation of infection	4 6	9 6	6 0
Thrombo embolism	0 8	2 3	1 0
"Addisonian-like" crisis	0	2 3	0
Osteoporosis and compression fracture	0	1 1	1 0
TOTAL	25 6	36.4	28 0

bra The marked demineralization of the osseous structures and further collapse of the 11th dorsal vertebra with bony bridging are clearly evident in Figure 5 6 B

Other side effects which have been reported include an increased tendency to clotting resulting in thrombophlebitis, decrease in glucose tolerance with the appearance of glyosuria, and aggravation of a pre-existing hypertension A list of the adverse reactions encountered in the author's series is presented in Table 5 3

The administration of corticotropin produces a hyperplasia of the adrenal cortex with increased production of adrenal hormones and an inhibition of endogenous ACTH Sudden withdrawal results in a temporary deficiency of endogenous ACTH Administration of the steroids also inhibits the normal production of corticotropin from the anterior pituitary and, in addition, leads to adrenal cortical atrophy In both instances, abrupt cessation of therapy results in a temporary state of adrenal insufficiency. Henneman reported 19 patients with acute withdrawal symptoms "In general the longer the period of cortisone therapy the more severe were the symptoms on stopping treatment " These symp-

toms may be alarming and in the event of a superimposed stress such as injury, infection or an operation, an Addisonian-like crisis may be precipitated One death occurred in our series in a manner which suggested acute adrenal insufficiency A second case responded to the intravenous administration of 400 mg of hydrocortisone given over a period of 36 hr

There is suggestive clinical evidence that a state of relative adrenal insufficiency may persist for long intervals following withdrawal of hormone therapy This has been illustrated by shock-like states induced by stress such as surgery The re-institution of steroid therapy before contemplating surgery and maintained for an adequate period usually ranging between 4 to 7 days, has been employed prophylactically in these instances

Choice of Preparation

Some clinical advantages based on differences in chemical structure and pharmacologic activity may be gained in special situations Corticotropin administered intravenously by slow infusion provides effective and rapid relief of the acute severe bronchospastic state Because it is active only when given parenterally, this agent is not suited for the general ambulatory treatment of the office patient "Anaphylactoid like" reactions encountered with the earlier preparations have become less common but still do occur even with the more highly purified material now available The long-acting corticotropin gel may be of some advantage in long term therapy with the adrenal steroids and in the "tapering off" process preparatory to discontinuing therapy

Although intravenous hydrocortisone is the agent of choice in states of acute adrenal insufficiency, the oral preparations of cortisone and hydrocortisone have been supplanted to a large extent by prednisone and prednisolone Although most of the adverse reactions observed with cortisone and hydrocortisone therapy have been encountered with these newer agents, the lack of salt and water retention and the diminished potassium loss at the usual therapeutic dosage level is an unquestionable advantage in the long term treatment of the ambulatory patient The psychologic benefit of an unrestricted diet, except for those patients

in heart failure, contributes in no small way to the general sense of well-being The effect on fluid retention when prednisone was substituted for cortisone in a patient with lymphatic leukemia, pulmonary emphysema and fibrosis is illustrated in Figure 5.7. Although on a low sodium diet with supplemental potassium chloride, a weight gain of 7 lb occurred during cortisone therapy. The substitution of prednisone was accompanied by a diuresis and weight loss of 8 lb with clinical improvement in dyspnea during the first week of treatment In a recent paper, Thorn raises the warning that reactions which result from increased glucocorticoid activity are more insidious than salt and water retention. The obstacles which must be anticipated in long term therapy are marked protein depletion, osteoporosis and diabetic potentiation. Certainly, the increased incidence of gastrointestinal complaints and the reactivation of peptic ulcer are of some concern

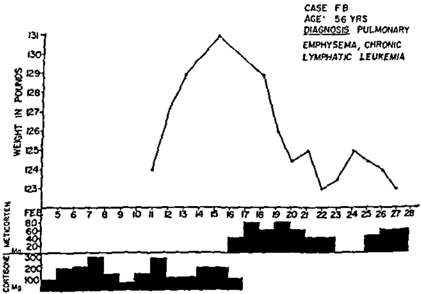


FIG 5 7 Although the diet and ancillary therapy remained unchanged, a weight loss of 8 lb. with clinical improvement in dyspnea occurred within the first week following the substitution of prednisone for cortisone in a patient with chronic lymphatic leukemia and pulmonary emphysema (Bickerman, H. A., Beck, G J, and Barach, A L J Chronic Dis, 2. 247, 1955)

requiring careful selection of patients and adequate antacid therapy

In any form of therapy, and especially one which is symptomatic, the benefits of such therapy must significantly outweigh the risks involved The chronically ill patient with severe pulmonary emphysema refractory to the conventional measures for relieving obstructive dyspnea presents no problem in weighing these theoretical considerations When the full program of treatment for pulmonary emphysema, which includes the use of bronchodilator drugs both orally and by aerosol, measures to facilitate bronchial drainage, such as potassium iodide and pressure breathing, oxygen therapy and breathing exercises, is ineffective in the adequate control of dyspnea, steroid therapy is indicated It must be emphasized however that the above measures which are discussed more fully in other chapters, should not be eliminated despite the temporary inhibition of symptoms by prednisone Since we have nothing better to offer this group, this calculated risk must be undertaken in the hope that, by tiding the patient over a critical period, life can be made less burdensome While the physician may be only "buying time", these agents frequently bring real relief which permits the more successful application of other measures designed to correct the pathophysiologic defects of pulmonary emphysema

A selective bibliography is given on page 234

Chapter 6

PHARMACOLOGIC THERAPY IN THE *MANAGEMENT OF PULMONARY EMPHYSEMA*

HYLAN A BICKERMAN, M D

Introduction

Because of the many gaps in our basic knowledge concerning the etiology and pathophysiology of pulmonary emphysema, a multitude of pharmacologic agents have been employed during the past century more or less empirically. The variable results of these therapeutic trials have given rise to considerable pessimism regarding the effectiveness of drug therapy in this disease entity Even before the newer concepts of respiratory function had been formulated, relief of dyspnea was clinically apparent in many patients with obstructive emphysema following the administration of bronchodilator drugs. The term "physiologic therapy" was originally employed by Barach to denote the basic principle of treatment which had as its purpose "the attempt to correct deviations from the normal functioning of the lungs and bronchi and to eliminate, wherever possible, reversible pathology in these organs" The administration of suitable agents specifically designed to restore towards normal some of the physiologic defects present in pulmonary emphysema constitutes an important link in the treatment of this disease

The claim has been made that drug therapy is only symptomatic and that the antispasmodics, expectorants, and sedatives commonly used have no effect on the course of pulmonary emphysema and may be more disturbing than effectual (Dawber and Hawes, Gordon) It is common experience to find that the patient with

pulmonary emphysema, like the asthmatic, has accumulated an entire pharmacopeia in his medicine cabinet into which he and his physician dip, at times irrationally, for relief Because of the disappointing results achieved, many of these patients are denied that measure of improvement in dyspnea and general well-being which could be provided by properly applied physiologic therapy. The author concurs with Barach who stated that such "physiologic treatment and recent developments in antibiotic therapy may transform a life of semi-invalidism into one in which substantial relief of the symptoms of dyspnea, cough and expectoration has been accomplished "

In the absence of any specific agent which could remedy the underlying disturbance in pulmonary emphysema at the etiologic level, the rationale of a therapeutic program must be based on the attempt to correct alterations in pulmonary physiology, eliminate infection, and slow or halt the progression of this disease The application of pharmaceutical agents in a practical program designed to improve respiratory function will be presented under the following headings (1) relief of bronchospasm, (2) facilitation of bronchial drainage, (3) sedation and relaxation, and (4) miscellaneous pharmacologic agents The treatment of infection, respiratory acidosis, and cor pulmonale with right heart failure will be discussed in Chapters 12, 14 and 15

Relief of Bronchospasm

It is the consensus of most investigators that obstruction to respiration plays a major role in the clinical picture of pulmonary emphysema Christie states that nearly all patients with this disease entity have a long standing history of asthma or chronic bronchitis. In some instances, bronchitis is one of the precipitating factors in the genesis of emphysema, and in others, bronchitis is acquired after the development of pulmonary emphysema. In either event, few if any of these patients are free from obstructive dyspnea, aggravated by the occlusive effect of mucus or paroxysmal episodes of bronchospasm By means of ventilatory function studies before and after effective bronchodilator agents, reversible obstruction to airflow has been detected in a majority of the

patients who may otherwise present no clinical evidence of bronchospasm

In a review of the physiopathologic aspects of chronic pulmonary emphysema, West and associates discuss bronchiolar obstruction and the reduction in pulmonary elasticity. The most important factor responsible for an increase in the work of breathing resulted from variable degrees of bronchiolar narrowing due to accumulated secretions, mural thickening, mucosal edema and bronchospasm More recent studies by Cherniack indicate that the beneficial effects of bronchodilator aerosols in patients with obstructive emphysema are manifested by a marked reduction in linear, but more especially in turbulent resistance to air flow with an increase in functional compliance. The partial relief of bronchial obstruction has been shown by Cournand to result in a sharp reduction in the oxygen "cost of breathing." This is more fully discussed in Chapter 11 by Alexander

Although many therapeutic agents have been employed effectively for the relief of bronchospasm, no single drug has proved entirely satisfactory Adverse side reactions and the development of tolerance have presented major stumbling blocks The judicious use of combinations of drugs, addition of sedatives and antinausea factors, and alternate routes of administration have been helpful in overcoming some of these obstacles. From a pharmacologic standpoint, the more common bronchodilator drugs are classified as adrenergic agents, anticholinergic substances and xanthine derivatives. Prior to the introduction of these drugs, the inhalation of smoke from burning stramonium leaves and nitrite powders provided relief in some instances, largely due to coughing and

pointing in the treatment of bronchospastic pulmonary emphysema

Adrenergic Agents

EPHEDRINE SULFATE

Ephedrine sulfate, either alone or in combination with theophylline, is perhaps the most frequently employed oral medication

for the relief of bronchospasm In the usual dose of 20 to 50 mg administered 2 or 3 times daily, it is often effective in mild episodes of bronchospasm At this dosage level, its administration appears to have a prophylactic value as well as a therapeutic effect The British advocate ephedrine as the preferred antispasmodic for routine use (Simpson, Whitfield) The dosage employed, however, is much greater than that commonly used in this country In a study on 51 patients, Herxheimer observed relief in 5 patients with mild bronchospasm at a dosage level of 60 mg Twenty-eight patients with severe obstructive dyspnea were markedly benefitted both subjectively and objectively, as measured by improvement in ventilatory function, with doses of ephedrine ultimately increased to 200 to 300 mg , 8 patients who obtained no relief were considered refractory These large doses were apparently well tolerated with only 3 patients showing evidence of toxicity

In our experience, doses of ephedrine in excess of 25 to 50 mg are accompanied by an increased incidence of adverse reactions including palpitation, excitation and insomnia Acute urinary retention is a distressing complication of ephedrine therapy in the older patient with prostatism It should be used cautiously, in small doses (20 mg) with aminophylline, in the presence of hypertension, and not at all in coronary artery disease with angina

The maximum bronchodilator effect is usually reached within one hour after ingestion and persists for a period of approximately 3 hours Tolerance to ephedrine is generally acquired fairly rapidly If given 3 or more times daily, its effectiveness often begins to decline by the end of the first or second week Increasing the dose may sustain the antispasmodic effect for a time, complete withdrawal for a period of 3 to 4 days, frequently enables the patient to regain his former responsiveness to this drug In our clinic, ephedrine is generally employed in doses of 15 mg combined with aminophylline 200 mg and sodium pentobarbital 15 mg * administered in the fasting state before breakfast and between 3 and 4 p m When tolerance becomes apparent, the drug is omitted for a period of 4 days to a week or more Less effective

* Made by the Irwin Neissler Co under the trade name Dainite (Day) Tablet

synthetic amines chemically related to ephedrine such as methoxyphenamine hydrochloride (Orthoxine) and methylethyl aminophenylpropanol (Nethamine) have been reported as producing a similar bronchodilator response as ephedrine but with fewer side reactions particularly in regard to central nervous stimulation (Segal, Hansel).

EPINEPHRINE

Although epinephrine has been employed for the relief of bronchospasm for over 50 years, its parenteral administration may be abused Self-medication by hypodermic injection is not recommended for routine use since these patients, in an effort to obtain sustained relief, often overtreat themselves, resulting in the rapid development of a refractory state. Doses in excess of 0 3 cc of the 1:1000 concentration are rarely necessary and are attended by a higher incidence of toxic reactions involving the cardiovascular and central nervous systems. Tremor, excitability, palpitation, abnormal cardiac rhythms and occasionally a shock-like state are among the more common adverse side effects encountered with larger or repeated doses These reactions are more fully discussed by Goodman and Gilman. The use of epinephrine subcutaneously in patients in the older age group with associated hypertension or coronary artery disease must be condemned. The value of parenteral epinephrine is for the most part limited to the treatment of the acute paroxysmal attack of bronchospasm. Slow release preparations, such as adrenalin in oil and aqueous epinephrine suspension (Sus-phrine), although at times helpful in recurrent attacks of bronchial asthma, have generally no place in the treatment of obstructive emphysema The inhalation of aerosols of epinephrine and related compounds has largely supplanted hypodermic administration However, a period of hyperdermic medication may be indicated in some patients who have used bronchodilator aerosols excessively.

The demonstration by Graeser and Barach that inhalations of aerosols of 1:100 epinephrine produced by a small particle-size nebulizer was effective in relieving broncho-spasm, has also resulted in the widespread use of aerosol therapy in assisting adequate

bronchial drainage and thereby aiding the control of bronchopulmonary infection. Although a discussion of bronchodilator aerosols with particular emphasis on the relative effectiveness of administration with and without intermittent positive pressure will be presented in Chapter 9, a description of the various preparations and techniques available will be discussed in this section on drug therapy.

The deposition of a fine bronchodilator mist on the mucosa of the bronchi and bronchioles of the respiratory tract presents many significant advantages over the parenteral use of these substances. Since the topical effect predominates with relatively little activity resulting from systemic absorption, toxic effects in the therapeutic dosage range are minimal. The ease of administration and its ready availability affords the patient with bronchospastic disease a measure of security not obtainable with injection therapy. However excessive use may result in increasing tolerance. This refractoriness can be overcome in some instances by the substitution of other sympathomimetic aerosols and by brief periods of withdrawal and substitution of other measures.

The nebulizers which, in our experience, have given the best clinical results in the administration of therapeutic aerosols are the Vaponefrin and De Vilbiss #40 which provide stable mists with a mean particle size of 2.5 μ and 3.0 μ respectively. Nebulizers which produce particles of 1.0 μ or less are not as satisfactory since much of the mist either passes into the alveoli and is absorbed or is lost in expiration with little deposition on the bronchial mucous membrane. Aerosols whose mean particle size is greater than 3.0 μ tend to deposit in the upper respiratory tract and oropharynx.

As little as 0.1 cc. of 1:100 epinephrine, 2.25 per cent racemic epinephrine (Vaponefrin), or 2.5 per cent racemic epinephrine with 0.5 per cent atropine sulfate (Dylephrin) nebulized by 4 to 6 compressions of the hand bulb of a Vaponefrin or De Vilbiss #40 nebulizer may abort or relieve a mild bronchospastic attack within a few minutes. The relief, however, may be only temporary and Barach and Richards have demonstrated that prolonged inhalations of dilute aerosols of epinephrine and phenylephrine

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(neosynephrin HCl) over a period of 20 to 30 minutes 3 or 4 time daily provided more effective bronchodilatation and broncho vasoconstriction in intractable bronchospastic states. Interrupte therapy by the Y-tube technique provides aerosol during th inspiratory phase of respiration The Vaponefrin nebulizer an Y-tube is illustrated in Figure 6 1. A mouth rebreathing ba technique is shown in Figure 6 2 Nebulization of solutions con sisting of 0.5 cc. of Vaponefrin, Dylephrin, Isuprel or Aerolon diluted with 2 cc of normal saline or a mixture of 1 cc. of 1 pe cent neosynephrin and 1 cc. normal saline is produced by oxyge flow rates of 4 to 5 liters per minute from a high pressure cylinder

FIG 6 1 A Vaponefrin nebulizer is illustrated with a Y-tube attachment which permits nebulization of the aerosol solution during inspiration when the open end of the Y is occluded During expiration, the oxygen stream bypasses the nebulizer

FIG. 6 2 Continuous nebulization of dilute bronchodilator solutions with the rebreathing bag technique is produced by a motor pump or high pressure oxygen at flow rates of 4 to 5 liters per minute

FIG. 6.3. The face tent may be used effectively in the continuous administration of bronchodilator, antibiotic or humidifying aerosols especially in patients too ill to perform the oral Y-tube technique. (Beck, G. J., Bickerman, H. A., and Marder, M. J., G.P. 10: 51, 1954.)

TABLE 6.1

Effect of bronchodilator aerosols on the vital capacity in patients with obstructive emphysema

Aerosol	No. of Cases	Vital Capacity Mean Change Over Control
		Per cent
Normal saline (placebo)	22	−0.2
2.25% Racemic epinephrine	30	+18.3
Dylephrin	56	+26.0

For home use, a small pump* has proven suitable although the flow rate is somewhat higher. The face tent, illustrated in Figure 6.3, has been useful in providing combined aerosol and oxygen therapy in the more seriously ill, uncooperative patient. The effect of epinephrine aerosols on the vital capacity of 108 patients with obstructive emphysema is illustrated in Table I. Spirographic tracings illustrating the effect of inhaling 0.3 cc. of Vaponefrin on the vital capacity and maximum breathing capacity of a patient with pulmonary emphysema is presented in Figures 6.4 and 6.5. Reduction in "trapping" and an increase in the expiratory velocity are evident in these tracings. A more complete descrip-

* Manufactured by the Medical Specialties Co., Boonton, N. J.

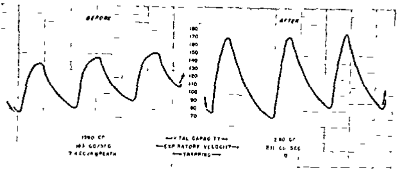

FIG 6 4 Spirographic tracing illustrating the effect of 2 25 per cent racemic epinephrine aerosol on the vital capacity of a patient with pulmonary emphysema The increase in expiratory velocity and diminished "trapp ng" is evident. (Bickerman, H A, and Beck G J, Ann Int Med, **36:** 607, 1952.)

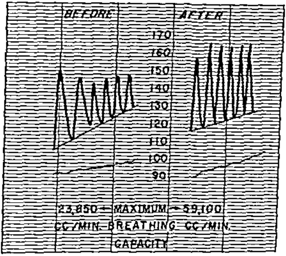

FIG 6 5 Maximum breathing capacity before and after 0 3 cc of 2 25 per cent racemic epinephrine (Vaponefrin) aerosol (Barach, A L, J. A M. A, **147:** 730, 1951)

tion of the rationale and techniques of aerosol therapy may be found in the reports by Barach, Bickerman, Segal and Abramson

The author is in accord with the views expressed by Baldwin, Cournand and Richards in which they state that the daily use of these aerosols over long periods resulted in considerable improve-

ment in ventilatory function with no evidence of serious toxicity or harm. More recently, Diglio and Munch reviewed the reports of other investigators on the long-term use of pressor aerosols and conducted a study in patients with hypertension, cardiac disease, thyrotoxicosis, and diabetes. They found no untoward effects following the inhalation of "many times" the therapeutic dose of epinephrine. Occasionally, too frequent use may result in dryness of the throat and tracheal irritation. This is more apt to occur with the larger doses of aerosols containing anticholinergic agents such as atropine. Improper use resulting in the swallowing of the aerosol solution may cause epigastric pain.

Isoproterenol (Isuprel, Aludrine, Norisodrine) is a valuable bronchodilator agent whose action on the smooth muscle of the tracheobronchial tree is similar to epinephrine. Although its acute toxicity appears to be less than epinephrine, clinical experience indicates that side reactions, principally tachycardia, are often more marked than those of epinephrine. Because of its effect on lowering blood pressure and peripheral resistance, its use may be preferred in patients with an associated hypertension. The most effective method of administration is by aerosol inhalation in doses of 0.1 to 0.5 cc. of the 1:200 dilution. As mentioned above, it is at times useful in patients who no longer respond to epinephrine. Dylephrin aerosol contains 2.5 per cent racemic epinephrine and 0.5 per cent atropine sulfate stabilized in an aqueous solution with propylene glycol. Aerolone compound consists of a solution containing Aludrine 0.25 per cent, cyclopentamine HCl 0.5 per cent and atropine 0.1 per cent for aerosol use. Sublingual tablets containing 10 mg. of isoproterenol and an inhalant powder are available. However, occasional depression of the T-waves on the electrocardiogram have been observed following its use. Clinical effectiveness of these routes of administration have been more erratic than with aerosols and the incidence of adverse reactions with adequate doses has been considerably higher, averaging about 30 per cent. These consisted of nervousness, tremor, dizziness, palpitation, precordial pain, nausea and vomiting (Lowell, Segal). Only a small percentage of patients experience toxic effects following inhalation of the aerosol (Goodman and Gilman).

The techniques of continuous nebulization of dilute aerosols of isoproterenol are similar to those described above. The addition of phenylephrine results in effective bronchovasoconstriction which reduces mucosal congestion and edema (Barach). Both Comroe and Lowell, in evaluating the bronchodilating effectiveness of Isuprel aerosol by ventilatory function tests, found that maximum relief of bronchospasm was not obtained since a further increase in vital capacity and maximal expiratory flow rate occurred following the intravenous administration of 0 5 gm of aminophylline

Anticholinergic Drugs

Since bronchospasm is mediated through the release of acetylcholine produced by stimulation of the parasympathetic nervous system, blockade of these bronchoconstrictor stimuli by anticholinergic agents would appear to offer a physiologic approach to the effective relief of bronchospastic states Of the naturally occurring belladonna alkaloids, atropine has been demonstrated to produce relaxation of the smooth muscle of bronchi and bronchioles However, it is considerably less potent than epinephrine as a bronchial antispasmodic *In vitro* studies by Castillo and de Beer, using a tracheal chain preparation, demonstrated that atropine had little antispasmodic activity but was highly potent in counteracting the smooth muscle spasm induced by acetylcholine. Other synthetic anticholinergic drugs such as Syntropan and Trasentine had a similar action, the antihistaminic, Benadryl, exhibited this atropine-like action to a lesser degree In contrast, epinephrine and aminophylline were capable of active dilatation of the untreated trachea.

In the previous section, it was noted that several aerosol compounds contained atropine in conjunction with adrenergic drugs These included Dylephrin and Aerolone Sjoerdsma and Dodge reported 8 of 11 patients with pulmonary emphysema had significant increases in vital capacity and maximum breathing capacity accompanied by symptomatic improvement following the intra-

tropate methylbromide (Pamine) and diethyl-methylammonium-bromide (Antrenyl) respectively. Diphenmethanil (Prantal) has been used in selected patients in our clinic. The intramuscular administration of 35 to 50 mg. of Prantal methylsulfate appeared to give effective relief of obstructive dyspnea (Barach).

Side effects of the anticholinergic drugs at the dosage levels used were for the most part mild and included dryness of the mouth and oropharynx, occasional blurring of vision, dizziness, and in isolated instances, urinary retention. Since these agents have a tendency to depress bronchial secretions, they are not suitable for continued use and should be employed with caution in patients with retained secretions who appear to have difficulty in raising thick, tenacious sputum. The "wet" asthmatic or emphysematous subject with bronchorrhea would be benefitted most by this drying action.

Xanthine Derivatives

The effectiveness of the xanthines in the treatment of obstructive dyspnea is based in part on their ability to relax the smooth muscle of the tracheobronchial tree. The most active member of this group in this regard is theophylline and its various salts. Bronchospasm refractory to epinephrine frequently responds favorably to theophylline. Dyspnea associated with cardiac failure may also show improvement with theophylline due, not only to bronchial dilatation, but also to an augmentation in cardiac output, decrease in venous pressure, and the promotion of a diuresis. All preparations of theophylline are irritating to the gastric mucosa and this important side effect often makes it difficult to administer the full therapeutic dose orally without the use of measures designed to decrease this gastric intolerance. This will be discussed below.

Although epinephrine and ephedrine have been generally recognized as valuable in the treatment of broncho-spasm, the effective use of aminophylline (theophylline ethylenediamine) in a program of remissive therapy has often been neglected. The excellent bronchodilator activity of aminophylline when given intravenously has been well documented. Patients with severe obstruc-

tive dyspnea who are refractory to the adrenergic compounds frequently obtain marked relief following the intravenous administration of 0.25 gm aminophylline in 10 cc. of diluent. This injection should be performed slowly over a period of 8 minutes and may be repeated in 15 to 30 minutes. Rapid administration has been accompanied by severe reactions and in some instances death due to the marked fall in cerebrospinal fluid pressure and venous pressure with inadequate right heart filling More prolonged bronchial relaxation in patients with severe distress can be accomplished by the infusion of 500 to 1000 cc. of 5 per cent dextrose in distilled water containing 0 5 gm. aminophylline. Two liters of solution may be given daily for 2 or 3 successive days. The rectal administration of 0 6 gm. dissolved in 20 to 30 cc. of tap water has been shown by Barach to provide effective relief without the danger of serious cardiovascular reactions In addition, this route offers a considerable advantage in providing a simple method of administration which can be performed by the patient or a member of the family using a catheter and syringe In our experience, aminophylline by suppository or intramuscular administration in doses of 0.5 gm has produced variable results This erratic effect on bronchospastic states probably results from *large variations in absorption and hence the plasma levels of* theophylline Intramuscular aminophylline is exceedingly irritating and may cause intense local pain which is only partially mitigated by the addition of 1 cc of 2 per cent procaine to the injection.

For the more prolonged relief of mild to moderate symptoms such as cough and exertional dyspnea, Barach found that the administration of aminophylline by mouth on an empty stomach was a valuable method of producing relaxation of the bronchi in a considerable number of patients with pulmonary emphysema A *dose of 0 2 gm. before breakfast and at 3 p m, with 0 3 gm* on retiring is the customary schedule employed in our clinic For the older patient with pulmonary emphysema, we generally find aminophylline preferable to ephedrine, especially at night, since it is less apt to cause excessive stimulation and wakefulness. Tolerance to aminophylline develops more slowly than to the

adrenergic substances, and there is no danger of acute urinary retention.

The most troublesome side effect of oral aminophylline is the *high incidence of gastric intolerance with nausea and vomiting* which limits the administration of effective therapeutic levels of this drug. Enteric coating, while materially reducing the incidence of these side reactions, results in impaired absorption and little or no therapeutic effect. Waxler and Schack found wide variations in the theophylline plasma levels after oral ingestion of enteric coated aminophylline tablets with many of the subjects failing to *demonstrate any detectable blood level*. *Truitt and his co-workers* determined that the effective plasma level of theophylline necessary for significant diuretic activity was 0.5 mg. per cent. Since bronchodilator activity parallels diuretic effect, it is not surprising that Segal, employing protection study techniques, found that comparable blood levels were required for relief of bronchospasm. In attempting to mitigate gastrointestinal intolerance to aminophylline and not interfere with absorption, aminophylline was combined with aluminum hydroxide 160 mg. and ethyl aminobenzoate 30 mg. (Cardalin).* Patients were able to tolerate 300 mg. and in some instances 600 mg. of aminophylline in this combination with relatively few side effects. The administration of these tablets resulted in a rapid appearance of theophylline in the blood as early as 15 minutes after ingestion with levels *persisting* for 9 hours. In a study by Beck and Bickerman, the plasma theophylline levels following the ingestion of 300 and 600 mg. of Cardalin were determined over a seven-hour period. This is illustrated in Figure 6.6. These levels are comparable to the theophylline levels obtained after the intravenous or rectal administration of 500 mg. aminophylline.

Combinations of aminophylline with ephedrine have been mentioned. Dainite (N.R.) consists of two tablets, the "Day" tablet has 200 mg. aminophylline and 15 mg. ephedrine, and the "Night" tablet, 300 mg. aminophylline, 30 mg. sodium pentobarbital and 25 mg. phenobarbital with ephedrine omitted. Both

* Cardalin and Dainite tablets (Irwin Neisler Co.) both contain these antinausea factors.

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tive dyspnea who are refractory to the adrenergic compounds frequently obtain marked relief following the intravenous administration of 0 25 gm. aminophylline in 10 cc. of diluent This injection should be performed slowly over a period of 8 minutes and may be repeated in 15 to 30 minutes. Rapid administration has been accompanied by severe reactions and in some instances death due to the marked fall in cerebrospinal fluid pressure and venous pressure with inadequate right heart filling More prolonged bronchial relaxation in patients with severe distress can be accomplished by the infusion of 500 to 1000 cc. of 5 per cent dextrose in distilled water containing 0.5 gm. aminophylline. Two liters of solution may be given daily for 2 or 3 successive days The rectal administration of 0 6 gm dissolved in 20 to 30 cc of tap water has been shown by Barach to provide effective relief without the danger of serious cardiovascular reactions In addition, *this route offers a considerable advantage in providing a* simple method of administration which can be performed by the patient *or a member of the family using a catheter and syringe* In our experience, aminophylline by suppository or intramuscular administration in doses of 0.5 gm. has produced variable results This erratic effect on *bronchospastic states probably* results from large variations in absorption and hence the plasma levels of theophylline Intramuscular aminophylline is exceedingly irritating and may cause intense local pain which is only partially mitigated by the addition of 1 cc of 2 per cent procaine to the injection

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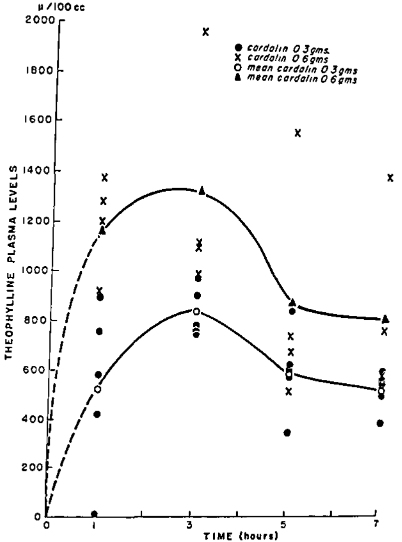

FIG 6 6 The plasma theophylline levels following the ingestion of 300 and 600 mg Cardalin (aminophyllin, aluminum hydroxide and ethyl aminobenzoate) exceeded 0 5 mg per cent over a 7-hour period (Bickerman, H A., Beck, G J, Itkin, S., and Drimmer, F., Ann Allergy, 11: 301, 1953)

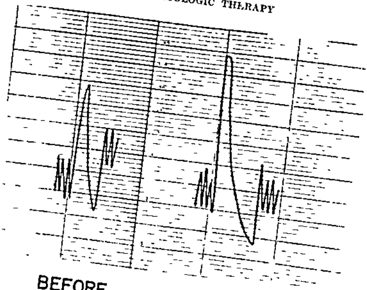

FIG 6 7 Spirogram illustrating the effect of "Day" tablet (aminophylline and ephedrine) on the vital capacity 1 hour after ingestion (Bickerman, H A, Beck, G J, Itkin S, and Drimmer, F, Ann Allergy, 11: 301, 1953)

contain aluminum hydroxide and ethyl aminobenozate The increase in the vital capacity one hour after ingestion of a "Day" tablet is illustrated in Figure 6 7 Nephenalin (N R) is a drug mixture composed of an outer coating containing 10 mg isoproterenol which is absorbed sublingually, with the remainder of the tablet consisting of theophylline 120 mg, ephedrine 25 mg and phenobarbital 8 mg for more prolonged effect through gastrointestinal absorption In an effort to augment therapeutic effectiveness by permitting higher dose levels orally, several new salts of theophylline are reported as causing less gastric irritation and having a more rapid rate of absorption than aminophylline (Brown, Dann, Katz) Among the preparations available for

clinical use are theophylline sodium glycinate, theophylline methylglucamine (Glucophylline N.N.R.), calcium theophyllinate, and choline theophyllinate (Choledyl N.R.). Differences in gastric tolerance and clinical value between these newer salts and aminophylline combined with antinausea factors have, in our opinion, been too slight to justify the added expense of some of these preparations In addition to the development of refractoriness, the long-term daily use of aminophylline prophylactically, may in some instances result in a cumulative effect with an increase in adverse side reactions This can be prevented by a program of intermittent therapy in which ephedrine is substituted for aminophylline for periods of a week or more The administration of aminophylline by aerosol or powder insufflation is clinically ineffective and may intensify bronchospasm due to local irritation

Other drugs have been reported as affording relief in obstructive dyspnea Although khellin (Visammin) produces relaxation of the bronchial musculature, both Silber and associates and Kennedy and Stock found it relatively ineffective in the treatment of pulmonary emphysema In addition, the high incidence of side effects, especially nausea, precluded its use in the majority of patients in our clinic Both nitrogen mustard and artificial fever therapy produced by the intravenous administration of typhoid vaccine (Kirk) or Piromen (colloidal dispersion of polysaccharides derived from *Pseudomonas aeruginosa*) have induced remissions in states of intractable bronchospasm refractory to the drugs mentioned above (Ayra, Waldbott, Knight) The mechanism of action has been attributed to a stimulation of endogenous adrenocorticosteroid secretion Prednisone has largely supplanted these procedures in the seriously ill patient refractory to conventional measures, although Kirk's typhoid vaccine is still occasionally employed in our clinic

Facilitation of Bronchial Drainage

In addition to bronchospasm, other factors are frequently operative in the production and maintenance of partial bronchial obstruction. The importance of inadequate elimination of bron-

chial secretions in the genesis of obstructive dyspnea is frequently neglected in the treatment of pulmonary emphysema An excessive production of mucus often occurs in these patients as a result of an allergic response to inhaled allergens, irritation of an edematous bronchial mucosa, chronic bronchial infection, or unknown factors In a number of cases observed in our clinic, cigarette smoking has not been as frequently implicated as the actual cause of a productive bronchitis as has been reported by other investigators The presence of these retained secretions provokes paroxysms of coughing which in turn serves to accentuate spasm of the tracheobronchial tree Because of poor muscular coordination and the "check-valve" mechanism described by Dayman, air flows produced by the cough in patients with pulmonary emphysema are largely ineffectual in evacuating the deeper air passages of tenacious mucoid or mucopurulent secretion Other physiologic mechanisms for the removal of these secretions such as the ciliary action of the lining epithelium are likewise impaired The consequences of bronchial obstruction by retained secretions are so serious as to warrant every effort both mechanical and pharmacologic to facilitate bronchial drainage Increased trapping with further overdistention of the alveoli results in progressive deterioration of the emphysematous state Interference with gaseous exchange in a patient who is already maintaining a burdensome ventilation, may precipitate acute respiratory insufficiency with carbon dioxide retention and acidosis, or sudden failure of the right heart with overt cor pulmonale

The mechanical and postural measures which aid in bronchial evacuation are discussed in Chapter 3 by Barach and Chapter 7 by Beck The following section deals with pharmacologic therapy such as expectorants and aerosols which facilitate the elimination of retained secretions

Expectorants

These drugs assist in the removal of secretion or exudate from the tracheobronchial passageways Tuft and Levin describe two mechanisms of action (1) secretolysis—liquefaction of the bronchial secretions, thereby making the sputum more fluid and less

viscid, and (2) excitomotor—stimulation of the smooth muscle of the bronchi to increased peristaltoid activity. Liquefaction is brought about by the actual secretion or excretion of the expectorant agent into the bronchial secretions with a lowering of the viscosity so that it becomes less tenacious The cough mechanism is related to the use of expectorants in clearing the upper bronchial passages of secretions. The tight bronchitic cough of pulmonary emphysema is frequently associated with a scanty production of thick, tenacious sputum. In the feeble or exhausted patient with impaired ciliary action and peristaltic contraction of the bronchiolar muscles, the cough may become ineffective in raising obstructing secretions Brown has classified the expectorants into 3 groups· (a) sedative, (b) stimulant, and (c) anodyne Of these, only drugs in the first category have been found the most useful in the treatment of emphysema This group, which includes iodides, ammonium salts, nauseants and demulcents, act to soothe bronchial inflammation by stimulating the secretion of additional mucus so that dried out plugs may be loosened from the bronchial wall, resulting in a more effective cough

Salts of iodine have been used for over a century in the treatment of bronchospastic states "Potassium iodide is one of the most valuable drugs for combatting intractable bronchial spasm and inadequate expectoration of viscid mucus both in bronchial asthma and pulmonary emphysema" (Barach) Iodide is rapidly excreted by the bronchial glands and can be detected in the secretions within 15 to 25 minutes after oral or intravenous administration (Tuft and Levin) The saturated solution of potassium iodide is generally employed and although it may impart a bitter, metallic taste, this has not proven too objectionable especially when given with milk An initial dose of 0.6 to 1 0 cc. four times daily after meals and at bedtime, provides effective expectorant action For patients who complain of gastric intolerance to the saturated solution, enteric-coated tablets (Enkide), or organic iodides such as Lipiodine and Triode may be used. The iodides may be given for long periods since tolerance rarely develops Nevertheless, the drug should not be prescribed for longer than is necessary once the cough has been "loosened." In a number of

patients who show continued benefit while receiving iodides, the dose may be lowered to 0.3 cc three or four times daily. Hobby has emphasized the importance of large doses of iodide to obtain effective expectorant activity He initiates therapy with 0 6 cc. of potassium iodide 3 times daily and gradually increases to a level of 2 0 cc. 3 times a day

The major side effects due to iodide therapy include skin eruptions, coryza, and painful swelling of the salivary glands In the event of such hypersensitive reactions, the drug must be discontinued Frequently, it may be reinstituted at a lower dosage level Rasmussen has recently described two cases in which iodide sensitivity was implicated in the causation of periarteritis nodosa Both patients had bronchial asthma and the possibility of periarteritis underlying the asthmatic state cannot be excluded Corticotropin and the adrenal steroids have been used successfully in the treatment of severe iodism (Waugh) The main contraindications to the use of iodides have been mentioned as pulmonary tuberculosis, and thyroid adenoma However, Hobby believes that potassium iodide is not contraindicated in pulmonary tuberculosis "The thinning out of the secretions produces more sputum and floats out bacteria already present, but it does not cause reactivation or spread of the disease "

Although the ammonium salts, chloride, carbonate, and citrate are probably the most commonly used expectorants, we have found them of little value in the treatment of pulmonary emphysema Their action is transitory and "it is not unlikely that some of the beneficial action ascribed to ammonium salts is in reality due to the ingestion of large amounts of water taken with these salts" (Goodman and Gilman)

Ipecac is the only member of the nauseant group which we have employed in our clinic, usually in patients who are hypersensitive to the iodides Perry and Boyd, and Basch and his co-workers found that ipecac induced a considerable increase in respiratory fluid secretion Ratner reported excellent results from syrup of ipecac in asthmatic children with bronchial obstruction who were resistant to epinephrine Ipecac also appears to relax the smooth muscle of the bronchi Syrup of ipecac is given in doses of 0 5 cc

4 times daily after meals and at bedtime. The only adverse reaction we have noted is the occasional complaint of nausea which may be prevented by lowering the dose When given to produce vomiting, it is at times of major value in eliminating retained bronchial secretions

The mode of action of potassium arsenite (Fowler's Solution) is obscure and although it is not an expectorant, it is presented at this point because of its administration in conjunction with potassium iodide Hansen-Pruss has reported the deleterious effects of inorganic arsenic in the treatment of asthma. Most of the patients in his series were seen 2 weeks to 2½ years after receiving the "Gay treatment," and the majority of these reported some form of gastrointestinal disturbance which usually appeared in 2 to 6 weeks after the onset of therapy. In several instances, the author and his associates have been impressed by the effect of small doses of Fowler's Solution in patients with intractable bronchospastic emphysema We have employed 0 2 cc 3 times daily for a period of 7 days followed by 0 1 cc. 3 times daily for an additional 7 days When benefit is clinically apparent, repeated courses have been given at intervals of a month or more.

Banyai and Cadden have reported on the effectiveness of carbon dioxide inhalations, 5 to 10 per cent concentrations with oxygen, in promoting bronchial drainage Its use is not recommended in pulmonary emphysema not only because carbon dioxide elimination is already impaired, but other, more suitable measures are available

Aerosol Therapy

Although the expectorant drugs, especially potassium iodide, are important adjuncts in aiding the elimination of retained secretions, three types of aerosols have been used to help liquefy these tenacious mucoid or mucopurulent secretions. They have been classified as humidifying, detergent, and mucolytic.

Humidification has generally been considered helpful in the treatment of patients with chronic respiratory disease This is particularly true in those sections of the country where colder weather means spending the major portion of the day in an artificially

heated room The combination of excessive dryness and dust which has accumulated about the steam radiators or in the hot air ducts do appear at times to perpetuate symptoms of obstructive dyspnea in patients with emphysema The use of the steam kettle was a relatively ineffective method of attempting to correct the low humidity. The inhalation of a mist produced by the nebulization of normal saline solution has been most useful in our experience Two to five cc of normal saline may be nebulized by the mouth rebreathing bag technique or into a face tent 4 times daily using a small particle size nebulizer of the Vaponefrin or De Vilbiss #40 type This provides a stable mist which is largely deposited in the bronchi and bronchioles and to some extent may help to loosen inspissated plugs of mucus in the lower respiratory tract

The rationale for the use of detergent or "wetting" agents was based on their ability to lower the viscosity of sputum Numerous investigators have pointed out that the local deposition of wetting agents will reduce surface tension and loosen retained mucus secretions from the mucosa by their emulsifying action (Ravenel, Farber and Wilson, Denton) Mild detergent agents such as alcohol, 5 per cent propylene glycol or glycerine, and zephiran chloride 1.5000 have been used by aerosol as vehicles for antibacterial or antispasmodic drugs for some time Following the enthusiastic report by Miller and associates on the use of a new nontoxic detergent, superinone, in the aerosol preparation Alevaire (superinone 0 125 per cent, glycerine 5 per cent, sodium bicarbonate 2 per cent), an extensive and controversial literature has accumulated Smessaert, Collins and Kracum reported that the sputum of patients with chronic respiratory conditions, including emphysema, became less viscid and easier to expectorate after 48 to 96 hours of Alevaire therapy, and Miller obtained good results in 10 of 11 patients with chronic asthma Frank, employing intermittent therapy 2 or 3 times weekly, could not demonstrate any consistent improvement In a controlled clinical trial of Alevaire in newborn infants, Briggs concluded that it seems unlikely that aerosolized wetting agents will in any way benefit infants suffering from atelectasis or hyaline membrane syndrome.

Preliminary studies with Alevaire aerosol in our clinic showed

that this material was irritating to the respiratory tract and that the increased amount of mucus produced was probably the result of this irritant effect Other investigators have remarked on the irritant nature of Alevaire suggesting that the alkaline pH in excess of 8 5 was responsible In substantiation of this, is the statement by Fabricant that "a hydrogen ion concentration near that normal to the mucous membrane is a matter of even greater importance for applications to the mucous membranes than the matter of isotonicity."

Our experiences with the mucolytic or proteolytic enzyme aerosols, Tryptar (crystalline trypsin) and Pancreatic Dornase (pancreatic desoxyribonuclease), have not been encouraging Using the recommended dose of 125,000 units of Tryptar dissolved in 3 cc of Sorenson's buffer twice daily, considerable irritation with pharyngitis and glossitis became apparent in the majority of patients by the third to fourth day of treatment. To a much lesser extent, this was true for Pancreatic Dornase Prince and associates report similar findings with trypsin aerosol in the treatment of asthma, and only 5 of 31 cases of chronic bronchial asthma with emphysema showed improvement in a series studied by Unger and Unger They reported 20 untoward reactions among 73 patients consisting of hoarseness, increased asthma, nausea, and rash about the lips Although Salomon and associates encountered no adverse reactions with Pancreatic Dornase, results in patients with chronic asthma or emphysema were not striking The reader is referred to two papers, one a review of enzymatic aerosol therapy by Farber and his co-workers and the other by Denton on various techniques of continuous nebulization in bronchopulmonary disease, for additional information Neither the detergent or enzymatic aerosols are generally effective in irradicating bronchial infection associated with pulmonary emphysema Suitable antibiotic agents, either by aerosol or other routes, must be administered

Sedation and Relaxation

In some respects, the treatment of severe obstructive dyspnea due to pulmonary emphysema resembles that of status asthma

Many of these patients are restless and apprehensive The lack of adequate sleep or nutrition initiates a vicious cycle in which labored respiration and dehydration combine to accentuate the retention of secretions, favor bronchospasm and thereby increase the obstruction to air flow This sequence of events results in an exhaustive state bordering on shock Rapid and effective measures are at times required if a fatal outcome is to be avoided Although it is generally accepted that heavy sedation is hazardous from a ventilatory viewpoint, some form of mild sedation is often desirable in the tense patient who finds it difficult to obtain adequate rest

In the past few decades, the barbiturates have become the most widely prescribed agents for sedation and hypnotic use Small doses of the shorter acting barbiturates are often incorporated into various drug combinations used in the treatment of chronic emphysema In higher dosages these drugs, like morphine, depress the respiratory center resulting in inadequate ventilation and respiratory acidosis Adriani and Rovenstine studied the effects of certain drugs upon the bronchi and bronchioles of excised lung tissue from animals and humans. They noted that cyclopropane, morphine, paraldehyde, and the sodium salts of Pentothal, Phenobarbital, Barbital, Amytal and Nembutal were bronchoconstrictors whereas ethyl chloride, chloroform and the ethers were bronchodilators Chloral hydrate has been recommended as the drug of choice for mild sedation It may be given in doses of 0 5 to 1 0 gm orally or by rectum at 8- to 12 hour intervals without fear of respiratory depression In special instances, where heavier sedation is desired in an effort to terminate intractable bronchospasm, 60 to 90 cc of ether dissolved in an equal amount of olive oil has been administered rectally as a retention enema This normally produces restful sleep with good relaxation for a period of 2 to 4 hours Certain precautions must be observed in the use of rectal ether (1) constant surveillance during sleep by a nurse, and (2) maintenance of a patent airway by positioning the patient on his side with the head of the bed flat A few preliminary reports have appeared on the use of chlorpromazine (Thorazine)

and meprobamate (Miltown). The clinical appraisal of these newer drugs as sedatives in the treatment of pulmonary emphysema must await further investigation.

There is universal agreement that morphine is contraindicated in such bronchospastic states as asthma and pulmonary emphysema Various authors have remarked on the deleterious effects of morphine which in several documented instances have resulted in death due to obstructive asphyxia or irreversible respiratory acidosis These effects are (1) central respiratory depression, (2) augmentation of bronchospasm due to cholinergic activity, (3) inhibition of glandular secretion of the bronchial mucosa, (4) diminution of striated muscle tone including the diaphragm and intercostal muscles, and (5) suppression of the cough reflex (Rackeman, Hobby, and Mitchell and De Jong) To a lesser extent, these effects may occur with higher doses of codeine In the range of 15 to 30 mg of codeine repeated at 4- to 6-hour intervals, we have encountered only minor side effects such as cough suppression and a "drying" action on the bronchial secretions

Prior to the introduction of the corticosteroids and, more especially, prednisone, meperidine hydrochloride (Demerol) was reserved for those patients with severe intractable bronchospastic emphysema who had become refractory to other forms of bronchodilator therapy Its use in proper dosage and under close supervision is still recommended as an excellent method of obtaining bronchial relaxation in special instances Pharmacologically, meperidine is anticholinergic and possesses a strong spasmolytic action on bronchial smooth muscle Yonkman and Herschfus and his associates reported effective relief by meperidine in patients with severe asthma This was substantiated by improvement in ventilatory function tests. The development of progressive lack of response to bronchodilator drugs in pulmonary emphysema presents a serious problem Several papers by Barach emphasize that one of the simpler methods of restoring sensitiveness to bronchodilator agents in these refractory patients is accomplished by a program of bed rest and the administration of meperidine for a period of 3 to 5 days This program consists of the intramuscular administration of meperidine 50 mg every 6 to 8 hours for a period of 4

days During this time, the bronchodilatory drugs such as ephedrine, aminophylline and epinephrine are discontinued Oxygen therapy may be instituted during this period in a manner to be described in Chapter 2 by Barach Responsiveness to the conventional bronchodilators is usually regained within 4 to 6 days When the program is to be carried out in the home, a tablet containing 50 mg Demerol is administered after each meal and at bedtime for a period of 4 to 6 days The patient must be cautioned to rest in bed for 1 to 2 hours after each dose of Demerol since vertigo and nausea are more apt to occur in the upright position

The experience in our clinic indicates that "if excessive doses of barbiturate drugs are omitted, meperidine does not produce respiratory depression but accomplishes satisfactory bronchial relaxation in most cases" (Barach) Since the dyspnea of pulmonary emphysema is a constant, chronic burden to the patient, the possibility of meperidine addiction is a real problem In view of this, it is essential that the program be restricted to a period of 4 to 6 days Oral Demerol, while not as effective as the intramuscular administration, presents less of a hazard in terms of addiction We have observed only mild side effects in our series consisting of dizziness, loss of appetite, nausea and occasional emesis In over 300 patients treated by Barach, no instance of respiratory depression or intestinal atony has been encountered with the program of meperidine therapy described above In the event that respiratory depression should occur, N-allylnormorphine (Nalline) has been demonstrated to anatagonize effectively the depressant action of meperidine In this connection, Stroud and associates reported that the combined administration of aminophylline with meperidine counteracted most of the respiratory depressant effects of meperidine Caffeine and amphetamine may also be used for this purpose

Miscellaneous Agents in Pharmacologic Therapy

Radioactive Iodine Therapy

After applying all of the recommended therapeutic procedures available for the management of pulmonary emphysema, there

are a number of patients with far advanced disease who have obtained little or no benefit and suffer severe respiratory distress at the slightest exertion Stimulated by the reports of Blumgart and his co-workers of the beneficial results in angina pectoris obtained by producing a state of hypothyroidism, a number of investigators have induced myxedema by means of I^{131} in patients with severe, intractable pulmonary emphysema The rationale of this therapeutic approach involves a lowering of the basal oxygen requirement which makes a relatively larger amount of oxygen available to the tissues for energy expenditure beyond the basal state Bercu and Mandell reported that 7 of 10 patients exhibited definite improvement subjectively and on standard exercise tolerance tests Ten of the 24 patients in a series studied by Hurst, Levine and Rich showed significant benefit A dose of 20 mc. of I^{131} was given followed by an additional 20 mc. two months later. This method of treating advanced emphysema is currently under investigation at our clinic and at the Mayo clinic

Carbonic Anhydrase Inhibitor (Diamox)

The carbonic anhydrase inhibitor, acetazoleamide (Diamox), has been reported as helpful in some cases of severe emphysema with respiratory acidosis Diamox produces an increased urinary excretion of sodium, potassium, bicarbonate and water, and a decreased excretion of ammonia Associated with these electrolyte changes, there is a fall in arterial pH and CO_2 content These changes are for the most part transient returning to the control levels after 2 to 3 days (Nadell) The plasma CO_2 content, however, may remain depressed during the period of drug administration Other than as a diuretic, the mode of action of Diamox remains obscure, and reports of the clinical effectiveness of this drug in patients with pulmonary emphysema uncomplicated by right heart failure have been conflicting Heiskell and associates demonstrated a consistent reduction in CO_2 combining power to which they attributed the symptomatic benefit observed. Lyons found that the reduction in CO_2 content was not always accompanied by a reduction in pCO_2, and Bell and associates noted variable results in their patients with severe emphysema and

respiratory acidosis, subjective improvement not being sustained In contrast to these reports, Schwartz, Relman and Leaf observed clinical improvement in half their series of patients with severe congestive failure due to cor pulmonale. This improvement coincided with a copious diuresis and an average weight loss of 15 lb The excellent diuretic activity of Diamox in patients with fluid retention has been noted in our clinic Two dosage schedules are employed (1) 250 mg of Diamox daily for 5 successive days of each week, or (2) 250 to 500 mg every other day. Although Diamox has been reported as an innocuous drug with a low order of toxicity, serious consequences may occur from the use of this agent in acute respiratory acidosis since a further lowering of the arterial pH may result in irreversible damage by superimposing a metabolic acidosis upon the existing acidotic state Further dis-

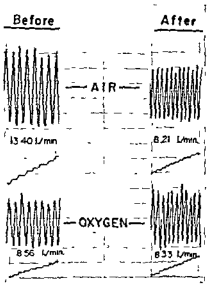

FIG 6 8 The spirographic tracings of a patient with Grade IV emphysema illustrating the marked reduction in resting minute ventilation and in the air-oxygen difference after six months of therapy, including bronchodilator aerosol, aminophylline, and diaphragmatic exercises (Bickerman, H A, and Barach, A L, J Chronic Dis, 1: 111, 1955)

cussion on the use of Diamox will be presented in Chapter 14 by Cherniack

The diuretic and cardiotonic agents employed in the treatment of heart failure associated with pulmonary emphysema will be discussed by Richards and Fishman in Chapter 15.

The integration of effective pharmacologic agents into a broad program of therapeutic management may help disperse the general air of pessimism with which the physician regards the treatment of pulmonary emphysema Measures designed to promote bronchial drainage, relieve obstruction to air flow, and eliminate infection of the respiratory system, when combined with properly administered oxygen therapy and special training in diaphragmatic breathing frequently achieves a considerable degree of rehabilitation even in patients with advanced disease. In a study by Barach and the author, the long term effects of such a program were evaluated in 33 patients with severe pulmonary emphysema (Grades III and IV) A marked reduction in the resting minute ventilation, a decrease in the air-oxygen difference when 100 per cent oxygen is substituted for room air during quiet breathing, and a significant increase in exercise tolerance were observed after six months of therapy The spirographic tracings of the pulmonary ventilation breathing air and 100 per cent oxygen in a patient with Grade IV emphysema before and after six months' therapy is presented in Figure 6 8 The striking reduction in the air-oxygen ventilatory difference and the fall in minute ventilation parallelled the degree of clinical improvement.

A selective bibliography is given on page 234

Chapter 7

METHODS OF AIDING BRONCHIAL DRAINAGE IN PULMONARY EMPHYSEMA

GUSTAV J BECK, M D

The physiologic mechanisms by which normal individuals eliminate secretions from the lungs are markedly impaired in pulmonary emphysema The sputum produced by patients with bronchial asthma is of viscid quality and especially difficult to expectorate, although the mucus is less tenacious in most cases of pulmonary emphysema The problem of its elimination during coughing and attempts at drainage is difficult and complex A brief review of some of the methods by which secretions can be expelled from the respiratory tract is helpful

CHARACTER OF SPUTUM

Although studies on the mode of production of allergic or mucoid sputum are not especially informative, observations of its character may be obtained by a Wright's and Gram stain of a representative sample The smear is inspected for white blood cells, eosinophils, bacteria, mucoid threads and epithelial cells In the presence of pus cells it is advisable to culture the sterilely-collected sputum on blood agar plates, and to perform a sensitivity study to determine the most advantageous type of antibiotics for therapy In our laboratory the sensitivity of all organisms present in the sputum is initially determined by placing small discs impregnated with various antibiotics on a blood agar plate which has been smeared with a representative sample of the purulent portion of collected sputum

Gross observation of the sputum generally provides a good

indication of the effectiveness of the therapeutic program used in the individual case The presence of a yellow or greenish purulent-looking sample warrants the administration of antibiotics in conjunction with special measures for bronchial drainage The need for expectorants is clear when the sputum is thick, tenacious or contains many plugs Among the expectorants most frequently advocated are iodine-containing medication, such as a saturated solution of potassium iodide or Lipiodine, syrup of Ipecac and ammonium chloride Their use is described in Chapter 6 by Bickerman The administration of liquefying aerosols is in our clinic confined to the inhalation of nebulized saline or a 5- to 10-per cent propylene glycole solution which is administered by means of the Vaponefrin rebreathing aerosol apparatus Oxygen or an air pump* provides the pressure necessary to achieve aerosolization. Tryptar and Alevaire, to lesser extent, do not have sufficient advantages to replace the saline or propylene glycole solution, since increased bronchospasm and dyspnea may follow their use in patients with pulmonary emphysema The consistency of sputum which does not show evidence of bacterial infection is usually more tenacious than that produced by patients with suppurative bronchitis In patients with pulmonary emphysema who have bronchial infections the thin purulent sputum is less difficult to expectorate than the viscid sputum which often follows successful antibiotic therapy, especially in cases with bronchial asthma.

The absence of sputum in patients with pulmonary emphysema is not always an indication of diminished severity of the disease, but rather, in some instances, of inadequate drainage and inability to raise secretions This situation is seen in pulmonary atelectasis, in which no secretions may be obtained but, nevertheless, plugging of bronchioles and bronchi occurs, producing, secondarily, marked interference with ventilation When bronchial drainage is facilitated by the use of expectorants or by physical means, expulsion of thick, heavy plugs of mucus is promptly accompanied by marked relief of symptoms and obviously improved ventilation Measures designed to dilate the bronchi, such as bronchodilator

* An air pump manufactured by the National Medical Specialties Co , Boonton, N J , has been found most satisfactory for this purpose

aerosols will promote expectoration of large amounts of plugs and freely flowing sputum in patients who had very little desire to expectorate. In the presence of severe bronchial infections, as demonstrated by the elimination of purulent plugs, antibiotic therapy will only be successful if adequate drainage is provided Failure to recognize this principle results frequently in failure of antibiotic therapy in patients who were treated with more than adequate amounts of antibiotics A subsequent course of therapy designed to improve aeration of the lungs and drainage, such as measures designed to increase bronchial diameter, as well as ventilate previously nonventilated areas of the lung by encouraging diaphragmatic breathing, mechanical means of eliminating secretions and the use of expectorants may improve dyspnea substantially even when smaller amounts of antibiotics are administered

NATURAL MECHANISMS OF BRONCHIAL DRAINAGE

Anatomical Position of the Bronchial Tree

Due to the erect position the antigravity effect on sputum and foreign bodies in the bronchial tree of humans is a great obstacle to adequate drainage of the more dependent portions of the lungs such as the lower and middle lobes Observations by Galoway and by Elwell that the trachea and larger main stem bronchi are tilted at an angle of 20 degrees away from the back and toward the chest wall as they ascend towards the neck, demonstrate one of the difficulties in obtaining adequate drainage by placing the patient simply in the supine position Under these circumstances the effect of gravity on sputum in the lower bronchi counteracts its flow toward the mouth If the thorax is tilted headward at an angle of 20° the trachea and large bronchi are at least at a horizontal position, thus overcoming the effect of gravity on sputum accumulated within it When the patient is placed on his stomach, in the supine position, however, the natural incline of the large airways greatly facilitates drainage Similarly, an elevation of the bed, with a headward tilt of the thorax of 22 to 25° when the patient is resting on his back would assist in promoting drainage of secretions from the bronchial tree

TABLE 1

Results of position of attention (after Lindhard)

	Number of Experiments	Residual Air	Vital Capacity	Total Capacity
1 Free standing position	9	1 61	4 42	6 03 L
Position of attention	8	1 86	3 68	5 53 L
2 Free standing position	2	1 27	5 96	7 23 L
Position of attention	2	1 60	4 87	6 47 L

The position of attention (military posture), as compared to the free-standing, slightly leaning-forward position, results in an increase in residual air at the expense of the vital capacity (Acta Med Scand, 120: 349, 1945)

comparison to a slightly bent forward posture. In patients with pulmonary emphysema, Barach reported a change in midposition toward inspiration when the patient moved from the erect to the leaning forward position A similar change is indicated on the spirometric tracings of Figure 7 1. The pulmonary ventilation under these circumstances decreases in many patients as diaphragmatic motion becomes more prominent. The preference for the leaning forward position by patients with pulmonary emphysema is then probably a natural compensating device which increases the bronchial diameter by assuming a more inspiratory position of the chest, it also promotes diaphragmatic breathing by decreasing the gravitational downward pull of the visceral organs, thereby increasing hilar ventilation and improving gas exchange, with the result that the minute volume of breathing is reduced with main-

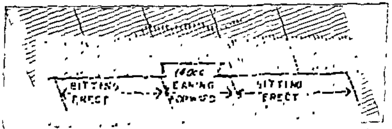

FIG 7 1. The chest of an emphysematous patient assumes a more inspiratory position (i e, 140 cc) when the patient leans forward from the sitting posture This thoracic volume increase is accompanied by widening of the bronchial lumen and, theoretically, better aeration of the alveoli

FIG 7 2 A patient with pulmonary emphysema standing in the erect posture displays, from left to right, paradoxical diaphragmatic motion by retracting the abdomen during inspiration and protruding it during expiration When leaning forward inspiratory protrusion and expiratory retraction of the abdomen signifying inspiratory contraction and expiratory ascent of the diaphragm, was easily achieved by the patient

An increase in thoracic circumference when leaning forward is accompanied by a change of the midposition of the lungs to a more inspiratory one, resulting in widening of the bronchial lumen and improved bronchial drainage (J Iowa State M Soc, July, 1954)

tenance of oxygen and CO_2 exchange in the lungs, (Fig 7 2) Thus the pathophysiological alterations in pulmonary emphysema apparently stimulate the patient to assume the leaning forward stance, and the increased diameter of the airways decreases the resistance in respiratory bronchioles and presumably lessens expiratory trapping of gases Perhaps, also, the mediastinum is pulled away from the posterior lung segments thereby aiding their ventilation

Consequently, improvement in aeration of many of the segments of lung, which are poorly ventilated in the erect position, occurs when the patient leans forward Because of the increase in bronchial diameter achieved by the assumption of this position,

air may bypass mucous plugs which obstruct poorly ventilated areas of lung tissue when the patient is in the erect position. The creation of an air cushion behind the plug due to expansion of previously collapsed areas of lung creates better conditions for expulsion of the plugs during coughing Higher volume flow rates during the natural cough in patients with pulmonary emphysema were also observed, when the patient was leaning forward Although the leaning-forward posture appears to create temporary relief of dyspnea and the elimination of secretions for the patient with pulmonary emphysema it does lead to increased inflation of alveolar walls

The gravitational forces exerted upon the diaphragm in the erect position in patients with emphysema also result in a more marked increase in inspiratory midposition, but without the benefit obtained by an augmented diaphragmatic motion. In normal individuals during the expiratory cycle the elevation of the diaphragm occurs as a result of recoil of the lungs. However, the diaphragm of the emphysematous patient remains at its inspiratory, i e, depressed level, because of various factors including impaired elastic recoil and alveolar overdistention

Bronchial drainage is also promoted by the leaning forward position because it produces elevation and, therefore, increased excursion of the diaphragm. The lower lobes, paravertebral gutters and hilar areas of the lungs are thereby exposed to a large proportion of the total minute volume of air and therefore are better drained of accumulated secretions. The increased diaphragmatic excursion produced by the leaning forward position also plays an important role in increasing the effectiveness of the natural cough of emphysematous patients. Clinically, less effort appears to be necessary in this position to achieve expulsion of secretions

THE HEADWARD TILT OF THE THORAX

Wade and Gilson observed that the largest increase in diaphragmatic excursion occurred when normal subjects were tilted at 45° head-down Their normal subjects had a marked rise headward of the diaphragm at a 45° head-down angle, with a decrease

in reserve diaphragmatic movement and a decrease in expiratory reserve air, with only slight decrease in total vital capacity

In the course of attempts at teaching diaphragmatic breathing to patients with pulmonary emphysema, it was found that the patient's upper thoracic movements during respiration could be abolished and diaphragmatic motion as well as lower costal respiratory movement selectively induced, by placing the patient's body in a headward tilt between 12 and 20° (Fig 7 3) It was apparent that the headward pressure of the viscera contributed to placement of the diaphragm into a more expiratory position and that resumption of the normal inspiratory position of the diaphragm occurred during its contraction Here, too, aeration of parts of the lungs previously poorly ventilated occurs In these cases stagnant secretions are prone to collect Improvement of aeration of these portions of the lungs results in better drainage of secretions from the bronchioles leading to them

Observations on a spirogram revealed that the patient's mid-position changes to a more expiratory one when his thorax is tilted headward from the sitting position (Fig 7 4) The marked relief of dyspnea observed in most patients with pulmonary emphysema in that position was associated with a lowering in the pulmonary ventilation and a slowing of the pulse rate In the study of ventilation and blood gas changes by Barach and Beck, the effects of the head-down position were compared with the sitting position The patients were generally placed at an angle of 16 to 20° with a pillow placed under the head to prevent flushing of the face A special jack was used for this purpose to lift the foot of the bed (Fig 7 5) Observation under the fluoroscope revealed a markedly increased excursion of the diaphragm in this position as the abdominal wall bulged forward during inspiration and relaxed backward and headward in expiration This normal pattern of diaphragmatic motion was restored in patients who, in the erect position, moved their diaphragms paradoxically upward in inspiration and downward in expiration A decrease in pulmonary ventilation of 22 per cent was observed on tilting from the sitting to the head-down position This decrease in minute ventilation was accompanied by a slight increase in arterial oxygen

change when the position was changed from the sitting to the head-down one In a patient who had a respiratory acidosis a marked change in pH from 7 27 to 7.44 occurred when the thorax was tilted headward (Fig 7.6)

It appeared, then, that, although these patients had assumed a more expiratory midposition, they were able to maintain or even increase their oxygen saturation to a slight degree with a reduced ventilation without significant CO_2 retention or acid shift of the pH This response may be compared to the early findings of Barach and later Bickerman and Beck and others in which the reduced pulmonary ventilation with 100 per cent oxygen was used as a test in patients with pulmonary emphysema Marked improvement in oxygen saturation took place but with retention of carbon dioxide and shift of pH to the acid side. However, with the thorax tilted headward the visceral impact upon the diaphragm promoted increased diaphragmatic motion, improved selective lower lobe and hilar ventilation to the point where hyperventilation was decreased, this result subsequently promoted a more effective cough and at the same time increased bronchopulmonary drainage.

Since the headward tilt of the thorax also counteracts the adverse effect of the tilt of the trachea, when the patient is lying on his back, a further benefit toward improved bronchial drainage in emphysematous patients is achieved

Increasing diaphragmatic motion of patients with pulmonary emphysema during all activities is important not only to obtain improved aeration of the lung, but also better drainage of the bronchial tree A training program is outlined in Chapter 3 by Barach. The head-down position has, in our experience, proved to be the most worthwhile method by which the patient can be made conscious of diaphragmatic motion Emphasis upon quiet respiration was first emphasized by Hofbauer and later by Barach. Since the head-down position offers an adequate degree of oxygenation without retention of carbon dioxide at a lowered ventilation, and improved drainage, it offers an excellent opportunity to show to the patient that no dyspnea need occur at even more reduced and

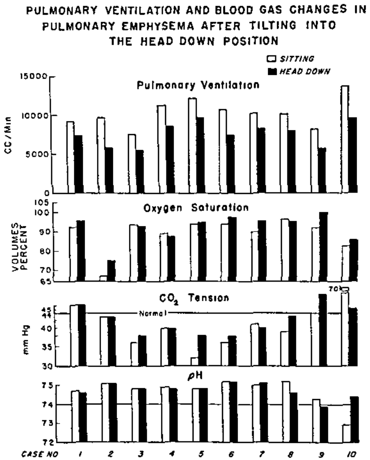

Fig 7 6 Improvement of selective lower lobe and hilar ventilation due to initiation of diaphragmatic excursion in the head-down position in patients with pulmonary emphysema results in a lowered minute ventilation without significant change in arterial oxygen saturation, pCO_2, or pH In one patient with respiratory acidosis the headward tilt of the thorax resulted in correction of the arterial pCO_2 and pH to normal Increased expectoration of bronchial secretions was observed in some cases (Am J Med, 16 55, 1954)

quiet respiration, and the first step toward teaching of predominantly diaphragmatic breathing.

THE SUPINE POSITION

Studies by Wade and Gilson in normal subjects showed no marked difference in diaphragmatic excursion in the erect or supine position during quiet breathing.

An analysis of data obtained by Wade during forced maximal inspiration and expiration led him to the conclusion that normal subjects are unable to exert voluntary control upon the extent of diaphragmatic excursion either in the erect or in the supine position He observed, however, that voluntary arrest of thoracic expansion is possible in some subjects In one patient in whom he measured diaphragmatic movement during quiet respiration the excursion increased from 4 to 5 cm when the patient made a conscious effort to perform predominantly diaphragmatic breathing Most physicians have observed diaphragmatic excursion as a result of the influence of the intra-abdominal pressure changes due to the position of the viscera relative to the diaphragm as well as diaphragmatic training Wade's opinion seems to be based on the fact that alterations in diaphragmatic excursion may be explained on the basis of changes in the vertical position of the chest during forced respiration To some extent his explanation may account for the findings of "paradoxical diaphragmatic" motion in the emphysematous patient However, in the head-down position in these patients, Barach and Beck noted that the weight of the viscera (as well as sandbags) upon the diaphragm played the major part in the marked increase in diaphragmatic excursion, as observable under the fluoroscope and by x-ray studies The appearance of increase in abdominal inspiratory protrusion and expiratory retraction, during the patient's quiet respiration in the head-down position appear to parallel the extent of diaphragmatic excursion, these findings are not contradictory to those of Wade since abdominal protrusion may not be an index of extent of diaphragmatic excursion with a *maximal degree of inspiratory effort* in normal subjects Abdominal protrusion is nonetheless a sensitive indicator of the presence of diaphragmatic

motion during quiet and moderate respiration The predominantly thoracic motion of the chest during respiration in emphysematous patients in the erect position may persist when they are placed in the supine position However, it was observed by Barach that training in diaphragmatic breathing could be facilitated in that position if a bag weighing 16 to 18 lb were placed upon the lower abdomen, again in an attempt to increase the intra-abdominal pressure to a point where it will push the diaphragm into a more expiratory position during expiration and increase diaphragmatic motion for improved lower lobe and hilar ventilation The resulting improved selective aeration of lung tissue results in better drainage of bronchioles from the previously nonaerated portions of the lungs However, this improvement is of a somewhat lesser extent than that achieved during the head-down position

The Ciliary Activity of the Bronchial Tree

Foreign matter and mucus are propelled toward the mouth by means of the ciliary action of small hairlike projections within the bronchial lumen Hilding has shown that a negative pressure of 40 mm of water is created distal to an obstructing foreign body moving mouthward along the airways of roosters One cannot discount the importance of such an active pull on an object within the tracheobronchial tree in the elimination of mucus in patients However, this mechanism is often completely abolished in patients with bronchial infection, such as frequently occurs in pulmonary emphysema and associated chronic bronchitis, and in patients with bronchiectasis, and, therefore, cannot be counted upon as an effective means of elimination of accumulated secretions, although it appears to be of great importance in subjects with intact ciliary activity

Peristaltic Action of the Tracheobronchial Tree

The presence of a muscular coat along the walls of the bronchial tree seems to indicate that an intrinsic mechanism exists which provides for contraction and dilation of that viscus This mechanism must, therefore, be considered as an important factor in the physiological consideration of elimination of secretions Reisseisen

demonstrated in 1822 by direct observation of the musculature of the bronchial tree that it apparently was arranged in a manner leading to a marked change in length and width of the bronchial tree and concluded that this musculature contributes an active part in the inspiratory and expiratory movement of the lung Under bronchoscopic observation, Jackson observed the inspiratory lengthening and expiratory shortening of the bronchi which he confirmed roentgenologically. Bullowa and Gottlieb introduced an opaque medium into the bronchial tree and observed a bellows-like action of the trachea and bronchi in anesthetized dogs and peristaltic motion of the bronchial musculature, which appeared to them sufficiently great to explain emptying of the bronchi without evoking ciliary motion W S Miller's observation of the anatomy of the tracheobronchial musculature led to the conclusion that tracheobronchial changes in diameter are mainly produced by active muscular contraction rather than by passive dilatation and narrowing of their lumen Hudson's roentgenographic tracings of the main stem bronchi and moderately large bronchi, following the instillation of a radiopaque substance in the tracheobronchial tree, indicated an active peristaltic contraction and relaxation of the musculature during inspiration and expiration, having the effect of cephalad propulsion in the course of expiration The alternate contraction and dilatation of the bronchial wall appeared to progress mouthward during the entire expiratory phase in a peristaltic manner He observed that this active expiratory mouthward propulsion of sputum is very effective in the absence of secretions in the normal bronchial tree, but diminishes in effectiveness as secretions and foreign material are contained for a prolonged period of time within the lumen of the bronchi From these studies they concluded that the muscular mechanism may be interfered with by prolonged infection or by stasis of secretions in the tracheobronchial tree. In bronchiectasis and longstanding bronchitis, the muscular peristaltic action is, however, improved. The peristaltic action is the primary mechanism of drainage of the bronchi and bronchioles Interference with this mechanism by infection, inflammation or destruction of the normal bronchial

architecture results in pooling of secretions, which then cannot be raised even by a most vigorous cough

THE NATURAL COUGH

Clinical observation of patients with bronchopulmonary disease results in the description of two types of cough (1) The patient takes a deep breath, closes his glottis, contracts his abdominal musculature and the levator and depressor muscles of the ribs into a rigid position, thereby increasing his intrapulmonary pressure Then he suddenly opens his glottis The high pressure distal to the glottis is suddenly released permitting a high volume flow rate to occur mouthward at the beginning of expiration The bronchi are relatively dilated and lengthened during full inspiration, in the post-glottis-opening stage they are abruptly narrowed and shortened (2) In conditions such as bronchial asthma, pulmonary emphysema and bronchiectasis, in which mucoid and mucopurulent material obstruct smaller bronchi, a paroxysm of coughing frequently takes place The initial portion of the paroxysm causes the production of high volume flow rates at the mouth whereas the final portions of the paroxysm show gradually decreasing expiratory volume flow rates At the glottis, the linear velocity of air in the cough is very high However, mucus may not be expectorated in cases with bronchospasm until the last series of coughs is produced at the end of the paroxysm The chest gradually decreases in size, producing a gradual expiratory decrease in the lumen of the bronchi, as has been observed during bronchoscopy and recently demonstrated roentgenologically by DiRienzo The high volume flow rates produced during the cough engender high air velocities primarily in the upper respiratory ...net and it is this high velocity which enables the sputum, which ...l been carried to the level of the larger bronchi, carina and lower ...chea by peristaltic action and ciliary action, to be carried to...s the mouth and to be expelled from the tracheobronchial ... During the glottis closure phase the intrathoracic pressures ...ed in most normal individuals varies between 80 and 110 ...of mercury In patients with bronchopulmonary disease

these pressures may be increased over 120 mm mercury. Since the expiratory muscles are fully contracted during this phase and since the rectiabdomini are *in the same phase of rigid contraction*, the intra-abdominal pressure follows fairly closely the intrathoracic pressure during this phase of coughing. Flow rates up to *12 liters per second* were observed at the mouth during the instant of opening of the glottis in normal subjects These high expiratory volume flow rates producing an air speed up to or sometimes higher than the speed of sound, *i.e.*, 732 miles per hour, propel sputum towards the mouth. When air has entered beyond the *obstructive material during the inspiratory phase, the sudden* contraction of the bronchi produces a high pressure gradient between the air trapped behind the plug and that in front of it, thereby pushing the mucus headward

In patients with pulmonary emphysema in whom the chest naturally has assumed the maximal inspiratory midposition, even during quiet breathing, it is difficult to increase chest volume substantially Therefore, the increase in diameter of the lumen during *the inspiratory phase of their cough over that in the expiratory* position of the patient is, by no means, as great as that observed in normal subjects The natural narrowing of the bronchial lumen due to bronchospasm and due to the increased alveoli-to-bronchiole pressure gradient only contributes to the emphysematous patients' inability to increase their bronchiolar drainage during their attempts at inspiration before the glottis opening phase of the cough The subsequent premature collapse of the bronchi during the glottis opening phase is the primary difficulty in moving sputum from the smaller alveoli towards the mouth Dayman has demonstrated in some patients with pulmonary emphysema by means of *high frequency recording equipment that their instantaneous* peak expiratory volume flow rates at times may be as high as those achieved by normal subjects during coughing The duration of the high volume flow rates were, however, of a very short order, mainly because the total volume of air expelled in the immediate postglottis opening phase in these patients is very small, as compared to the volume expelled by the normal subjects He concluded from these findings that a premature collapse of

the bronchi was responsible for the sudden cessation of volume flow at high rates during the cough of emphysematous patients, and that it was this interference during the expiratory phase which was in part responsible for the difficulty in eliminating secretions during coughing

Any procedure designed to prevent the narrowing of the bronchi, and thereby their premature collapse during the expulsive phase of the cough, would appear to increase its effectiveness The clinical observation on emphysematous or asthmatic patients of the greatly increased facility for eliminating secretions following the administration of bronchodilator aerosols was found experimentally to be accompanied by an increase in expiratory volume flow rates over that prior to the inhalation of the aerosol (Fig 7 7) Instructions to the patient on the use of bronchodilators such as 2 25 per cent racemic epinephrine (Vaponefrin), *n*-isopropylartere-

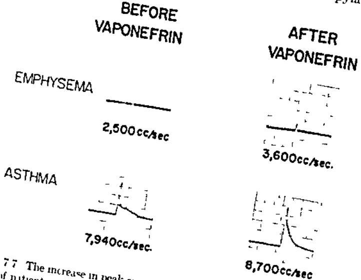

Fig 7 7 The increase in peak expiratory volume flow rate during the natural cough of patients with pulmonary emphysema and bronchial asthma, occurring after the administration of a bronchodilator aerosol is accompanied by more effective elimination of secretions

nol (Isuprel) or racemic epinephrine-atropine mixtures (Dylephrine) prior to coughing are necessary to assist them in the elimination of their tenacious secretions The increased viscosity of the sputum also interferes greatly with the ability to raise the sputum from smaller bronchi towards the mouth because of its tendency to cling tenaciously to the wall of the bronchi in which it is contained Because of inadequate pulmonary ventilation and a decreased amount of air carried into the lungs of the emphysematous patient during inspiration as well as the premature collapse of the smaller bronchi, there is a marked reduction in volume flow rates measured at the mouth during even the most vigorous cough created by patients with pulmonary emphysema, even though simultaneous intrathoracic measurements show markedly increased intrathoracic pressure Interesting studies conducted by Dayman revealed that the intrathoracic pressure does not fall abruptly from its high levels to those of atmosphere, but that there is a gradual decreasing intrathoracic pressure drop to atmospheric level The initial high volume flow rate is produced by the initial fast drop of pressure; subsequently a milking action of the bronchi occurs when the chest is somewhat in the expiratory position, which is produced by the narrowing of the bronchial lumen and the gradual expulsion of air from the alveoli and small bronchioles beyond it It is this milking action that has been held responsible for much of the effectiveness of the cough. In conclusion, one cannot overemphasize the importance of both the inspiratory and expiratory phase of coughing in achieving adequate elimination of foreign substances from the tracheobronchial tree. Interference with either one of these phases will lead to inadequate elimination and total obstruction of the tracheobronchial lumen

Mechanical Devices Designed to Improve Elimination of Secretions

EXSUFFLATION AND THE MECHANICAL COUGH CHAMBER

The problem of adequately eliminating secretions in patients with pulmonary emphysema as well as those with chronic bronchitis, bronchiectasis, bronchial asthma and pulmonary insufficiency due to neurological disorders prompted studies by Barach.

Beck, Bickerman and Seanor to devise means of imitating the natural cough by mechanical means and thereby permitting more adequate drainage of the bronchial tree Because the correlation of the efficiency of the natural cough in normal subjects with that of patients with impaired cough mechanisms showed that a marked reduction in expiratory volume flow rates took place in the latter group, it appeared that a device designed to increase expiratory volume flow rates to the level of those achieved in normal subjects would be helpful Introduction of air into the chest was attained by means of a positive pressure breathing device and the rapid expulsion of air simulating the glottis opening phase of the cough by means of a rapid pressure drop from a high intrathoracic pressure to the atmosphere or below In initial experiments, using a standard tank type respirator, the process of "exsufflation" was achieved by means of inspiration produced by a gradual pressure build-up of an intratank negative inspiratory pressure to -40 mm mercury by means of a vacuum cleaner motor A large valve was opened up suddenly when this peak pressure had been attained permitting the intratank pressure to rise to that of the atmosphere The natural recoil of the lung and the expanded thoracic and diaphragmatic musculature produced a sudden expiratory decrease in chest volume, thereby, creating a high expiratory volume flow rate The pressure drop achieved in exsufflation occurred within 0 06 seconds Studies by Bickerman and associates in dogs showed that the tracheobronchial lumen of anesthetized dogs during the peak inspiratory pressure of 40 mm mercury within the tank respirator increased 44 1 per cent at the tracheal level and 85 2 per cent at the primary bronchial level over that during normal quiet expiration The maximal increase in the cross-sectional diameter, observed in the smaller bronchi, averaged 100 per cent It was evident that during this inspiratory distention of the bronchial diameter air would be permitted to bypass any obstruction within the tracheal lumen Since the inspiratory flow rates, produced by the gradual increase in pressure to 40 mm mercury within the tank respirator, were of a very low magnitude at a time when the diameter of the bronchi gradually increased no danger of pushing foreign matter or sputum

distal to their location during the inspiratory phase existed. These studies were conducted roentgenographically following the injection of a thick contrast medium, *i.e.*, a thorotrast-mucin mixture within the tracheobronchial tree. A rapid diminution of the dogs' chest volume during the drop of pressure from 40 mm mercury to atmosphere during 0.06 seconds in exsufflation produced the elimination of the contrast medium In normal subjects application of exsufflation by Barach, and associates, revealed expiratory volume flow rates approximately 60 per cent of those recorded in the vigorous cough of normal subjects. Patients with poliomyelitis revealed increases of their flow rates of 145 per cent during exsufflation and exsufflation combined with manual compression of the lower thorax

In a parallel development in the production of a mechanical cough, the patient resided in a mechanical cough chamber; a sudden decompression of ⅕th of an atmosphere within a compartment in which the head and neck were enclosed was produced with a simultaneously increased pressure momentarily applied to the chest wall and abdomen The immobilizing lung pressure chamber was modified to provide a sudden decrease in pressure in the head-end from 110 mm mercury above the atmosphere to atmospheric pressure in 0 08 seconds, resulting in swift expansion of gases within the lungs A close fitting baffle around the neck produced an initial pressure in the body compartment 40 mm. higher than in the head-end Studies in animals by Bickerman and associates revealed rapid elimination of thick thorotrast-mucin mixtures from the tracheobronchial tree of animals Subsequent studies in human subjects by Barach and Beck showed good elimination of secretions by means of this method

EXSUFFLATION WITH NEGATIVE PRESSURE

Exsufflation with Negative Pressure (E W N.P.) was subsequently found to be the most effective method for adequate elimination of bronchial secretions This technique is an extension and also a simplification of exsufflation as previously described Gradual inflation of the chest is produced by means of a vacuum blower unit, the positive pressure end of which is connected with

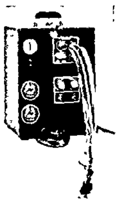

FIG 7 8A

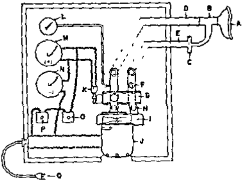

FIG 7 8B

FIG 7 8A E W N P with double hose and filter attachment A mouthpiece or a mask may be applied to the patient

FIG 7 8B. Schematic drawing of E W.N P.. During the inspiratory phase the fan (I) blows air through the valve (G), the tubing (E) and the bacterial filter (C) to the mask (A) which is placed over the patient's face The time of inspiration is controlled by the delay switch (M), the pressure by the relief valve (H) and the volume delivered to the patient by the butterfly valve (F) At the peak of inspiration the solenoid (K) rotates the valve (G) so that the fan (I) of the motor blower unit (J) is swiftly connected to the tube (D) which is connected with the mask (A), through the T tube (B), to the patient, producing a pressure drop of from 60 to 80 mm mercury in 0 02 seconds The duration of expiration is controlled by delay switch (N) The motor and rotating valve are independently turned on by switches (P) and (O), respectively (This model of E W N P, the Cofflator, is manufactured by the O E M Corporation, East Norwalk Connecticut)

a mask to the patient A peak pressure of from 20 to 40 mm mercury is used to inflate the patient, similar to the intratank pressure inflation of the patients in exsufflation At the instant at which the peak inspiratory pressure is reached, a valve within the E W.N P (Fig 7 8) suddenly is switched to the negative pressure side of the vacuum blower, thereby producing a reversal of flow in the mask and a pressure drop to 40 mm of mercury below the atmosphere in 0 02 seconds The negative pressure of 40 mm. mercury below the atmosphere then is maintained for a period of 1 5 to 2 seconds The duration of the inspiratory phase

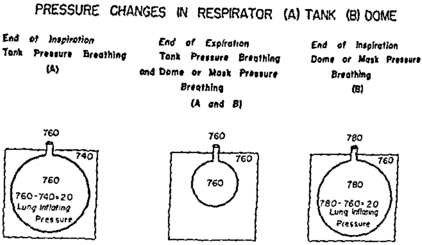

FIG 7 9 The effect of application of negative pressure around the chest of a patient whose body is contained within a tank respirator is similar to positive pressure applied at the head by means of a dome or mask provided the mean pressure and shape of the pressure curve are the same In this hypothetical instance the lung inflating pressure is 20 mm mercury, whether the intra-tank pressure is lowered to 20 mm below the atmosphere, or the intra-dome pressure is raised to 20 mm mercury above the atmosphere. A minor difference is that when supra-atmospheric pressure is applied with a mask, air density is higher than when negative pressure is applied around the body. (Am J. Med Sci, 274: 169, 1952)

is from 2 to 2 5 seconds depending upon the volume of the patient's chest Since the observations of Maloney and Whittenberger and those of Beck, Barach and Seanor were made, it has become evident that the inspiratory phase, as obtained by a negative intratank pressure during exsufflation was similar in its cardiovascular and respiratory volume effects to the inspiratory positive mask pressure produced by E W N P However, the rapid pressure drop from 40 mm above atmosphere to 40 mm. below atmosphere, a total of 80 mm mercury, in 0 02 seconds achieved with exsufflation with negative pressure produced volume flow rates which were as great as those achieved during normal subjects' most vigorous natural coughs when measured at the mouth. In patients with bronchopulmonary disease, including pulmonary emphysema, bronchial asthma and bronchiectasis, as well as patients

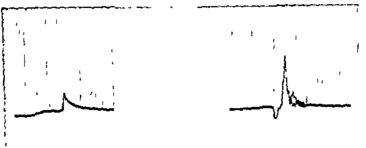

Fig 7 10 The peak expiratory volume flow rate of a patient with pulmonary emphysema during E W N P was 9 230 cc /sec as compared to that of 5 860 cc /sec during his own natural cough

with respiratory insufficiency due to chronic spinal poliomyelitis, an increase in expiratory volume flow rates often twice that, produced during their own most vigorous natural coughs, was observed by Barach, Beck and Smith (Fig 7 10) In studies conducted on anesthetized dogs, thorotrast-mucin mixtures were eliminated within one hour from the tracheobronchial tree, foreign bodies placed within the lungs of dogs for a period of three days were eliminated shortly following the application of E W N P

The intramask pressure changes occurring during E W N P are of a completely different configuration from those obtained by all other devices used for the treatment of pulmonary emphysema E W N P is primarily a positive-negative pressure breathing apparatus, the outstanding feature of which is the pressure drop from the peak inspiratory to the expiratory phase in 0 02 seconds Although it has been claimed that intermittent positive pressure breathing devices have a rapid expiratory pressure drop which has a physical effect on expulsion of sputum, the magnitude and swiftness of the fall within the mask in no instance approached that observed with E W N P (Fig 7 11) In our experience they have little value as an aid to elimination of secretions by physical means

The achievement of high expiratory volume flow rates during

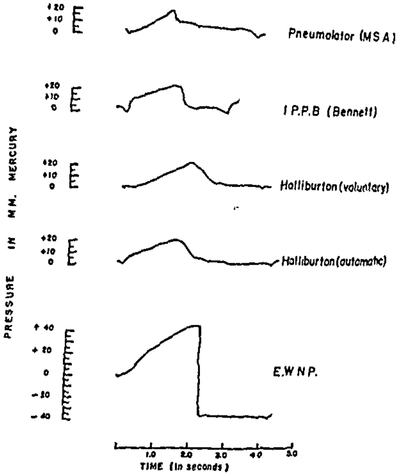

FIG. 7 11 The shape of the mask pressure curve is illustrated for various types of supraatmospheric intermittent pressure-breathing devices and for exsufflation with negative pressure In the use of E W.N.P. the duration of the expiratory pressure drop is 0 02 seconds as compared to 1 second or more with the I.P.P.B apparatus The mean pressure over a complete respiratory cycle in the subject tested was 2 5 for the Pneumolator, 7 2 with the Bennett, 5 1 for the Halliburton used with spontaneous respiration, 6 7 when used as automatic resuscitation and −6 9 mm Hg with E W.N.P The low negative mean pressure with E W N P. is due to a 2-second exposure to −40 mm Hg When the expiratory cycle is reduced

Hg pressure due to the abrupt cessation of pressure during expiration and the duration of the negative pressure selected. (Am J. Surg, 89: 372, 1955)

the initial expiratory phase in patients with bronchopulmonary disease during the application of E W N P was accompanied by greatly increased diaphragmatic excursion (Fig 7 12) During their natural coughs, patients with pulmonary emphysema or poliomyelitis have little or no, sometimes even paradoxical, excursion of the diaphragm Normal subjects, in contrast, have a diaphragmatic excursion of from 6 to 10 cm During E W N P, excursion of the diaphragms of emphysematous patients was obtained approaching that observed during the cough of normal subjects This increased diaphragmatic motion was thought to be one of the factors responsible for the increased elimination of secretions in patients with bronchopulmonary disease

The cardiovascular effects of E W N P were those of a positive-negative pressure device Although there was a slight increase of the venous pressure as measured in the anterior cubital vein, this increase was less than that of other devices used for positive pressure ventilation, such as the tank type respirator or I P P B mask apparatus, when applied at pressures ordinarily used in the treatment of patients There was an increase in pulse rate and only minor variable changes in arterial systolic and diastolic blood pressure during the application of E W N P over those in the control period The electrocardiogram revealed changes due to rotation of the heart at the peak inspiratory pressure

Because of the usefulness of E W N P in the treatment for retained secretions during postoperative states, intragastric pressure measurements were conducted to obtain an index of intra-abdominal pressure changes Although intragastric pressures exceeding 90 mm mercury were nearly always obtained during a vigorous natural cough, they did not exceed 40 mm mercury during E W N P in any of the subjects tested (Fig 7 13) Clinically, postoperative patients who were unable to cough naturally because of wound pain were treated effectively and painlessly with E W N P It may be, therefore, concluded that E W N P is a safe and comfortable method of aiding patients with abdominal wounds to eliminate secretions

The use of E W N P on conscious patients with bronchopulmonary disease is most satisfactory if their full cooperation can

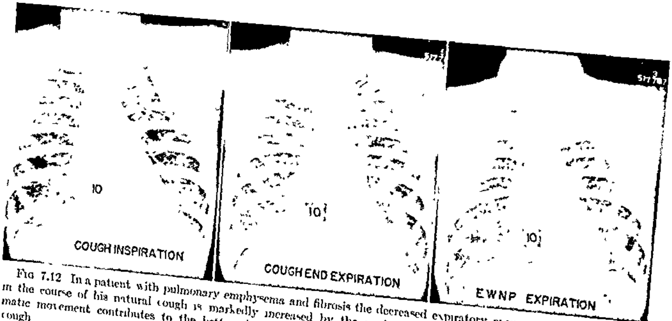

FIG 7.12 In a patient with pulmonary emphysema and fibrosis the decreased expiratory excursion of the diaphragm in the course of his natural cough is markedly increased by the application of E.W.N.P. This increased diaphragmatic movement contributes to the better elimination of secretions during E.W.N.P. than during the patient's own cough

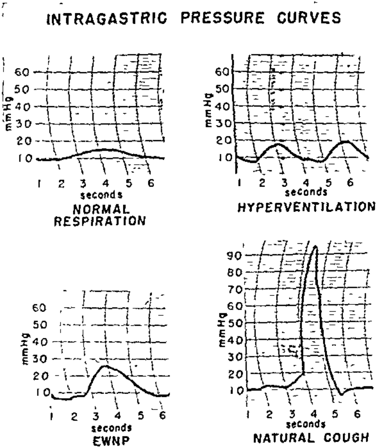

FIG 7 13 The intragastric pressure reflecting the intra-abdominal pressure, is considerably lower during E W N P than that produced by the patient's own cough It is only slightly higher than that produced during hyperventilation

be enlisted in using the device In the absence of the patient's cooperation the procedure fails in its purpose to assist the expulsion of secretions The expiratory volume flow rates of patients in whom E W N P is used successfully are relatively high, whereas it is only the same as in their natural cough in those who cannot cooperate The patient is asked to relax completely during the

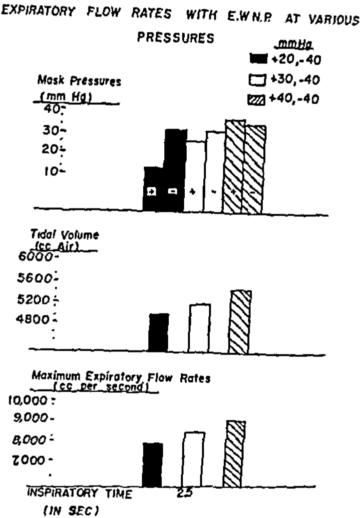

FIG 7 14 Peak expiratory volume flow rates during E.W.N.P., measured at the mouth, are increased as the total pressure drop from the maximum positive inspiratory to the maximum negative expiratory pressure is increased The tidal volumes moved during the expiratory phase in normal subjects increase proportionally to the pressure drop.

inspiratory phase, permitting a volume of air proportional to pressure head of 20 or 30 mm mercury supplied by E W N P enter his lungs passively (Fig 7 14) He is asked to keep his glot open and not to inhale actively, or more swiftly than the rate which the air is supplied to him by E W N P When the rapi reversal of pressure from the positive to the negative side occurs expiration should also be passive, expiratory volume flow rates achieved at the mouth in these circumstances are also proportional to the degree of pressure drop In patients with respiratory paralysis due to neurologic disease or in unconscious or anesthetized patients, sputum is carried directly into the pharynx or mouth, sometimes even into the mask applied to the patient Conscious patients with pulmonary emphysema, bronchial asthma or bronchiectasis are usually aware when sputum is carried by E W N P into their trachea, larynx or pharynx It then may be coughed into the mouth immediately following the procedure by a slight spontaneous cough or a swift expiration Usually five respiratory cycles with E W N P are sufficient to produce the desired effect This may be repeated 10 to 15 times for each session, 3 to 4 times daily

Because of our observations of occasional overdistention of the stomach in unconscious patients with relaxation of the cardiac sphincter of the stomach, due to introduction of air by E W N P into the esophagus, the placement of a gastric tube prior to the procedure in these patients has been recommended

The administration of bronchodilator aerosols should precede each treatment in patients in whom an element of bronchospasm is detected Expiratory volume flow rates produced by E W N P have been found to be higher and its clinical effectiveness appeared to be greatly enhanced following bronchodilator administration (Fig 7 15)

Roentgenographic observations have shown the great effectiveness of E W N P in the presence of atelectasis Within one session of mechanical coughing increased aeration of atelectatic segments may be found This is accompanied by clinical signs of improved aeration such as the appearance of breath sounds and increased resonance over the affected areas In those instances the pro-

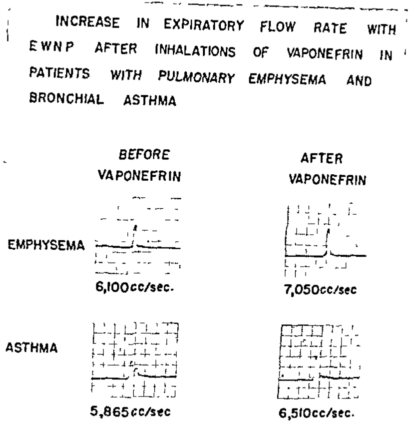

FIG 7 15 The administration of bronchodilator aerosols before the use of E.W N P *results in higher mechanically induced peak expiratory volume flow* rates and improved elimination of secretions in patients with pulmonary emphysema and bronchial asthma, with productive chronic bronchitis or bronchiectasis

cedure is accompanied by the elimination of plugs of mucoid, *mucopurulent and, in longstanding atelectasis, frequently blood* tinged plugs of secretions Relief of dyspnea, cyanosis, fever and disappearance of signs of mediastinal shift may then occur

Since large volumes of air are moved during each respiratory cycle of E W N P., signs of hyperventilation such as tingling in the extremities and dizziness, should be watched for. Five respiratory cycles in most instances are not accompanied by these symptoms The ability to induce hyperventilation by means of

E.W.N.P., however, is very useful in the treatment of patients with pulmonary emphysema, who have progressed into respiratory acidosis (lowered pH, high pCO_2) due to ventilatory depression by undue use of sedation, high concentrations of oxygen in the inhaled air, broncho-alveolar infection or cardiac insufficiency (see Chapter 14 by Chernack).

Williams and Holaday, in patients immediately following abdominal operations, were able to demonstrate a transient marked lowering of the arterial pCO_2, at times an increase in arterial pO_2, and a rise of the pH toward a more alkaline side during E.W.N.P. therapy, in patients with frank respiratory acidosis.

Although the use of the tank type respirator and various mask positive-pressure breathing devices have been described to relieve respiratory acidosis in emphysematous patients, exsufflation, using a 40 mm. negative tank pressure during inspiration, which is suddenly dropped to atmosphere by means of a valve attached to the side of the respirator has been described as more effective by Chernack. Both E.W.N.P. and exsufflation, when used in patients with bronchopulmonary disease with respiratory acidosis have, of course, the advantage of increasing markedly the elimination of secretions at the same time.

Expiratory Compression of the Lower Thorax and Bronchial Drainage

Barach in Chapter 3 on restoration of diaphragmatic breathing describes a manoeuver of intermittently compressing the lower ribs and elevating the diaphragm, while the patient performs an expiration through pursed lips. The amount of residual air trapped in the overdistended alveoli may be reduced thereby and the expiratory reserve air and the total vital capacity increased by this procedure considerably. Expiratory lower thoracic compression and elevation of the diaphragm results also in the expulsion of sputum with much greater ease than during the patients' own natural coughs. The pressure applied externally to the lower chest and diaphragm in short and swift strokes during expiration, in some ways imitates the paroxysmal contraction of the thoracic and diaphragmatic musculature during the patient's own cough

or the negative pressure phase in the mask of E W.N P. This manoeuver is helpful in the patient's *elimination of secretions* when applied during the patient's slow quiet expiration against pursed lips and, *also, immediately prior to the glottis opening* phase of his own cough It is carried out after inhalation of bronchodilator aerosols

Pneumoperitoneum as a Means of Increasing Bronchial Drainage by Improving Ventilation

The ideal *method of obtaining* improved ventilation and drainage in patients with pulmonary emphysema is one which permits *the placement of the patient's chest and diaphragm into a more* expiratory position thereby increasing diaphragmatic excursion. Pneumoperitoneum, a method which enables the patient to carry on this type of ventilation while in the upright position would seem therefore of marked therapeutic value. In 1924, Reich introduced pneumoperitoneum for the purpose of elevating the diaphragm in the treatment of pulmonary emphysema He observed that the administration of from 300 to 500 cc of air intraperitoneally provided marked symptomatic relief in this disease with disappearance of dyspnea and cyanosis, improvement of complicating bronchitis and reduction of attacks of bronchospasm because of increased bronchial drainage A generalized marked improvement of his patients was noted subjectively and objectively He studied the effect of pneumoperitoneum on diaphragmatic motion roentgenographically (orthodiagraphy) and found that increases in diaphragmatic range of from 1 to 6 5 cm of the right diaphragm

aphragm occurred from 1 to 4 5 cm on the right and from 0.5 to 3 5 cm on the left He was able to correlate the improvement of diaphragmatic excursion with the degree of elevation of the leaves to a more expiratory position He observed that pneumoperitoneum affected the right hemidiaphragm to a greater extent than the left His pulmonary function studies reveal an increase in tidal air of from 15 to 25 per cent as a consequence of pneumoperitoneum An increase in oxygen saturation of the capillary

blood of from 7 to 8 per cent occurred during pneumoperitoneum treatment

Piaggio Blanco and his associates advocated the repeated administration of large amounts of oxygen, 2,000 cc with each refill, and noted in their series an improvement in the effectiveness of coughing and ease of expectoration, increase in vital capacity and improvement in subjective feeling of the patient Gaensler and Carter induced pneumoperitoneum by the administration of from 300 to 1,000 cc of air and studied the standard pulmonary function tests before, during and after treatment by pneumoperitoneum Their findings were as follows a definite increase in vital capacity occurred in the majority of the patients studied, with a mean per cent increase of the predicted vital capacity from 59 2 to 69 5 per cent, with values ranging from 54 to 87 per cent of the predicted The tidal air did not appear to be significantly changed after treatment The expiratory reserve air was greatly *reduced before treatment in all patients and was not changed by* the treatment, a 24 per cent increase over the control value in inspiratory reserve was observed during pneumoperitoneum The residual air over total capacity ratio which varied before treatment from 45 1 to 71 8 per cent was dramatically reduced by pneumoperitoneum from a mean of 58 per cent to 45 8 per cent during pneumoperitoneum The maximum breathing capacity showed a marked change following pneumoperitoneum Although the value was only 33 2 per cent of predicted in the group before pneumoperitoneum, it increased to 43 per cent of the normal predicted value during administration of pneumoperitoneum A test of ventilation during walking at a required rate showed a marked improvement subjectively and a decrease in walking ventilation in one-half of the patients while it remained unchanged in the others during pneumoperitoneum administration

It appeared from their studies as if an increase in efficiency of alveolar mixing with a decreased tendency to hyperventilation may have occurred Studies of oxygen saturation in three patients revealed no change in oxygen saturation in one patient and slight to moderate increase in oxygen saturation in the other two Although no increase in oxygen saturation occurred in one patient

after exercise, the other two patients revealed markedly improved saturation, when walking, after pneumoperitoneum had been administered Two patients revealed a decrease in arterial carbon dioxide tension and one of these showed a marked decrease in carbon dioxide tension after exercise when pneumoperitoneum was administered Comparison of these physiologic data and clinical changes confirmed the original studies by Reich of a high degree of correlation between clinical improvement and laboratory evidence of improved pulmonary function. Kory and his associates, in an extensive study of the pulmonary function changes and cardiovascular effects of pneumoperitoneum in pulmonary emphysema, also demonstrated increased diaphragmatic excursion following the procedure, the degree of which, however, they could not correlate with clinical improvement. Whenever such improvement occurred an increase in inspiratory capacity, reduction in total capacity, residual air and RA/TC ratio was observed, confirming the findings of Gaensler. Similarly, an increase in arterial oxygen saturation and decrease in carbon dioxide retention occurred In one patient in whom cor pulmonale and marked pulmonary hypertension accompanied severe pulmonary emphysema, a considerable decrease in pulmonary artery pressure accompanied the improvement in blood gases following pneumoperitoneum A uniform decrease in cardiac output occurred in the emphysematous patients following the procedure.

Observations by Beck, Eastlake and Barach on the changes in venous pressure during pneumoperitoneum therapy in pulmonary emphysema revealed a marked consistent fall or no change in venous pressure in those patients who derived excellent benefits from pneumoperitoneum In three patients in whom a rise in venous pressure during the administration of pneumoperitoneum was observed, the procedure had to be discontinued because of respiratory embarrassment. Figure 7 16 demonstrates the venous pressure changes in two patients, one of whom had a poor clinical response to pneumoperitoneum with an increase in the venous pressure, in the other a fall in venous pressure occurred concomitantly with clinical improvement Figure 7 17 depicts the changes in venous pressure occurring during the administration of various

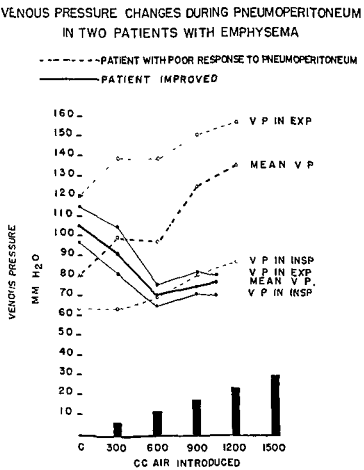

FIG 7 16 In the patient in whom a progressive fall in venous pressure followed introduction of air into the peritoneal cavity, clinical improvement was conspicuous In the other patient a rise in venous pressure took place, which indicated that the amount of air introduced was not accompanied by increased diaphragmatic motion and, therefore did not relieve dyspnea (Dis Chest, 22: 130, 1952)

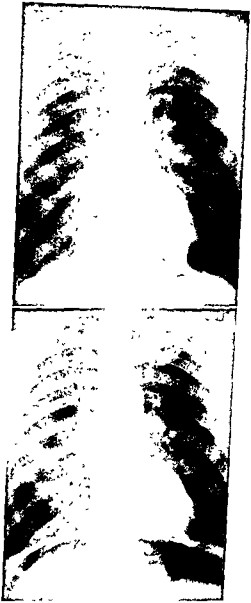

FIG 7 18 The intraperitoneal introduction of air favorably alters diaphragmatic function, i e, increased expiratory ascent, subsequent improved contraction and increased total excursion In a patient with pulmonary emphysema selective hilar and lower lobe ventilation improved bronchial drainage by increasing the effectiveness of coughing

mospheric level The observation of the fall in venous pressure during pneumoperitoneum parallels the findings of Alexander during the application of an abdominal belt

It appears as if the decrease in venous pressure, reflecting the decrease in intrapleural pressure, is a good indication of the effectiveness of pneumoperitoneum in patients with pulmonary emphysema It seems to indicate a better degree of retractability of the lungs produced by the elevation of the diaphragm to a more expiratory position

In patients in whom the venous pressure becomes elevated following the administration of air into the abdominal cavity, the degree of diaphragmatic motion appears to be inadequate, either due to atrophic changes in the diaphragm, inadequate retractability of the lungs, or inadequate diaphragmatic training or a combination of these factors It is conceivable that this decrease in retractability of the lungs is accompanied by a rise in venous pressure similar to that observed by Barach, Martin and Eckman during positive pressure breathing, with a decrease in return of blood to the right heart and a slowed circulation time This would result in a stagnant type of anoxia and contribute to dyspnea and interference with proper elimination of secretions. It was also observed that in patients in right ventricular insufficiency, a rise in venous pressure would occur when pneumoperitoneum was administered This may be in part a result of the inability to empty the right ventricle under these conditions of increased intrapulmonary pressure Gillanders similarly observed that no rise in venous pressure would occur in patients with uncomplicated emphysema when manual pressure was applied to the abdomen, whereas a marked rise appeared when the patients with emphysema were in right-sided heart failure The adverse effects of I P P B in these cases are commented upon in Chapter 10 by Miller, Fowler and Helmholtz

Pneumoperitoneum, similar to the application of a belt to the lower abdomen, will be only as effective in increasing the selective ventilation of otherwise poorly ventilated areas of the lungs and accomplishing their proper drainage as its capacity to improve diaphragmatic motion; therefore, it appears of great importance

that patients in whom pneumoperitoneum is administered should be well trained in increasing their range of diaphragmatic excursion From our observations as well as those of Banyai and Reich, one must conclude that, in the treatment of pulmonary emphysema, the amount of air introduced into the abdominal cavity must be kept at a much lower volume that one would ordinarily use in the treatment of pulmonary tuberculosis

Observations by Gaensler of the effect of pneumoperitoneum in patients with respiratory acidosis in lowering the carbon dioxide tension of the arterial blood and raising the pH as well as marked symptomatic improvement of these patients from the clinical effects of their respiratory acidosis seem to be a clue to the presence of improved selective hilar lower lobe ventilation, similar to that observed in the studies of Barach and Beck of the head-down position in the presence of respiratory acidosis

A full description of the technique of pneumoperitoneum may be found in the book by Banyai. The administration of pneumoperitoneum in our laboratory is usually performed by means of the Tycos pneumoperitoneum apparatus A number 19 needle is inserted into an area previously anesthetized with novocaine over the left midportion of the abdomen, avoiding any tympanic areas or abdominal scars. Using initially a syringe, a test for resistance to introduction of air is made by pushing the plunger in slightly and observing its rebound The entrance of the abdominal cavity is noted when the plunger can be freely lowered in the syringe During the introduction of the needle through the abdominal wall, slight suction is applied intermittently to determine if the needle has entered a blood vessel After the needle is inserted into the peritoneal cavity, air is gradually introduced by means of the Tycos apparatus until the desired amount for elevation of the diaphragm to a more expiratory, but not to the maximal expiratory position, is achieved Not infrequently, right-sided, and sometimes, left-sided shoulder pain occurs during that procedure This pain gradually subsides after continued pneumoperitoneum therapy On this regimen, reintroduction of air is usually necessary in from 7 to 10 days It has been observed that when pneumoperitoneum therapy is carried on over a prolonged

period of time the amount of air necessary to elevate the diaphragm increases because of a gradual relaxation of the abdominal wall When the needle reaches the peritoneum one can observe the normal variation of intra-abdominal pressure of from −4 to −2 cm of water with respiration

If the precaution of frequent testing of the needle at the time of introduction into the abdominal cavity by means of suction on the plunger of the syringe is performed, the incidence of air embolism is extremely low Although pneumoperitoneum is usually a safe procedure, one may, rarely, encounter, even with the greatest care, massive air embolism and death during initial pneumoperitoneum The procedure should be performed only by physicians well-trained in the technique

A selective bibliography is given on page 234

Chapter 8

AEROSOL THERAPY IN THE MANAGEMENT OF BRONCHOPULMONARY INFECTION, INCLUDING USE OF EXSUFFLATION

EDWIN RAYNER LEVINE, M D

It is perhaps not an exaggeration to say that bronchial or, more properly, bronchopulmonary infection, is present in almost every case of emphysema This may be said even though many of the customary criteria of infection are lacking. The blood count, sedimentation rate and temperature may all be normal and the productive cough, generally associated with bronchitis, may be entirely absent But there are times when the temperature is elevated and the blood picture is that of infection A constant and spasmodic cough is present although expectoration is difficult. Auscultation reveals, however, that secretions are present in the lungs.

The acute episodes are so dramatic that it is generally said that emphysema is marked by recurrent bronchial infection A more accurate statement is that bronchopulmonary infection goes through stages of acute exacerbation and remission, but that it is present as a part of the overall syndrome. This infection had much greater significance than its toxicity, whatever that may be, would indicate By its very presence, certain physiologic changes occur which interfere with basic functions of the cardio-respiratory system

The first and most obvious of these is the impairment of the airway by secretions and by edema of the mucosal wall The obstruction may be partial or complete, and its duration bears a very direct relationship to the viscosity and volume of the mucopurulent material The size and location of the particular bron-

chial tube is another determinant of the degree of obstruction, since mucosal edema of a small tube will occupy more of the lumen and less secretion is required to fill it completely The current of air passing through a small bronchus or bronchiolus is likewise minute and, in the emphysematous patient, is at times absent or nearly so This may and does result in retention of secretion in the small bronchi and bronchioli for long periods and creates the picture of progressively increasing obstruction of these small airways

A second mechanism which occurs simultaneously and adds to the retention of secretion is bronchospasm, occurring as a result of constant irritation and overcontraction of the bronchial musculature on expiration Such contractions have been shown to be irregular in nature producing localized constrictions as well as generalized narrowing of bronchi In fact both types of bronchoconstriction may occur side by side in the same individual The result of either is retention and a failure of expulsive mechanisms A secondary result is that such bronchospasm may continue through inspiration as well adding further of serious interference to the patency of the airway

Both internal obstruction and constriction of the bronchi interfere with the expansion and contraction of the lung itself, reflected not only in the movements of the chest but in the excursion of the diaphragm Since the lung does not retract as fully as normally the diaphragm cannot rise to its resting position Thus, when inspiration begins the diaphragm is lower with a smaller downward excursion This may progress to the point where the diaphragm is fixed in the depressed position

A third situation is present which affects both ventilation and the elasticity of the lung parenchyma, namely, the presence of infection in the lung as well as in the bronchi. The alveoli may become involved by direct extension down the lumen of the bronchi The parenchyma becomes infected to a greater extent by extension through the walls of bronchioli to the interalveolar spaces which are contiguous The latter type of infiltration is the more serious because it is more difficult to detect, harder to eliminate and because it increases the rigidity of the parenchymal

structure The resultant loss of elasticity diminishes both the volume and the velocity of air passing through the bronchi of the region with impairment of the mechanisms responsible for elimination of secretion that may be present.

Accompanying this complex picture is cough, always troublesome and spasmodic in nature, frequently causing more damage and interference than the imperfect benefit it provides of partial bronchial clearing The conditions previously discussed operate to impair the efficiency of cough as a mechanism for expulsion of bronchial contents Edematous mucosa, bronchospasm and the secretion itself obstruct the airway while the diminution in lung elasticity so diminishes the flow of air that even in apparently vigorous cough, the velocity of the air current is relatively slow, especially in the small bronchi where much of the obstruction is situated

The result is that in the patient with emphysema there is not only bronchopulmonary infection, but retention of secretion deep in the bronchial tree Because of the nature of emphysema and the physiologic mechanisms which are set up, secretion is retained whether or not the patient coughs and whether or not the cough appears productive

Treatment of this infection follows the principles of management of infection and bronchodilatation which have been discussed in previous chapters of this volume. In many cases, because of the duration and chronicity of the condition, it is necessary to use the direct approach of combined aerosol therapy and exsufflation with negative pressure

Aerosol therapy accomplishes certain definite ends It is an ideal method of administering bronchodilator drugs when rapid improvement is desired, often an essential part of treatment. In addition, aerosols furnish a vehicle and a technique for topical application of antimicrobial materials directly to the infected mucosa of the involved bronchi The third beneficial effect is related to the material of the aerosol itself, which being introduced into the tracheobronchial tree as airborne particles, remains to add liquid to the bronchial secretions and enables them to be more easily eliminated

The pathologic changes in emphysema, both anatomic and physiologic, make the use of an aerosol a logical approach to the management of bronchopulmonary infection in this condition As in all chronic inflammations, the actual blood supply to the infected area is diminished This, again, is demonstrated by the frequent absence of signs of infection in the blood picture and the normal level of temperature Consequently, especially in the clinically quiescent stage, antimicrobial drugs carried by the blood stream may have little effect unless the organisms in question are particularly sensitive to the drug used

When antimicrobial drugs are administered by aerosol there is an opportunity for the medication to reach all areas that are reached by air The droplets settle on the mucosa to inhibit the further growth of bacteria present, and probably actually destroy the sensitive strains

It is true that the infection is not only present on the surface, but also exists in the submucosal regions, which are in part ultimately reached by local absorption and by the blood concentration achieved by alveolar absorption As demonstrated by Barach, Olsen, Segal, Levine and others, and as borne out in the actual experience of many workers, this type of treatment is very effective in this type of infection

The lymph and blood channels of the bronchi are to some extent isolated from the areas of chronic inflammation which drain into the bronchial lumen As the aerosol destroys the activity and eventually the bacteria on the mucosal surface, the balance which has been established is destroyed There is less irritation and inflammation of the mucosa, permitting a more normal lining With less infection the body defenses regain an advantage needed to suppress inflammation In bronchoscopic studies made on such patients, the initial picture is of reddened, inflamed mucosa throughout the entire field After four weeks of aerosol therapy, the mucous membrane appears grossly normal with isolated reddened, inflammatory areas which later disappear It would seem that the clearing of the bronchial infection is not a uniform process, but proceeds locally wherever the infection is reduced

The trachea and major bronchi receive most of the aerosol

when large sized particles are produced However, with an average particle size of 2 5 μ (Vaponefrin nebulizer) and 3 0 μ, (No. 40, Vilbis), deposition on the smaller bronchi takes place, with correspondingly high sputum levels, as seen in Chapter 6 by Bickerman It follows also that those portions of the lung which receive most of the ventilatory air current will receive most of the aerosol In the patient with emphysema, since ventilation is irregular in distribution, the actual *amount of the aerosol which reaches the* diseased smaller bronchi is variable For this reason, the aerosol must be sufficient in potency, frequency and must be continued for a sufficiently long time to accomplish its purpose

Penicillin is the best antimicrobial drug for general use. As in other chronic bronchial infections, it should be used in solution containing 50,000 units per cc One or two cc or more of the solution may be employed in a single treatment. Although all organisms found in the bronchi are not sensitive to penicillin, it has been found that most of the bacteria actually causing trouble are penicillin sensitive The remainder are generally of low pathogenicity *and frequently are not responsible for any of the changes* mentioned above

In exceptional cases, in which gram negative or other penicillin resistant organisms are present, the addition of *100* mg. of streptomycin per cc to the penicillin solution is an effective *means of* controlling the infection

Whether water or normal saline is used as the solvent seems *immaterial since* there is no noticeable difference when using either one If the patient is sensitive to penicillin, as an increasing number of people seem to be, other antimicrobial drugs can be used Polymyxin and tyrothricin are sometimes effective, but have a rather limited scope and may be troublesome in long *term* administration Most of the broad spectrum antibiotics are rather

[illegible] I have however found Erythro-

imunating

effective

when staphylococci are an important part of the bronchial *flora*

One of the objections to aerosol therapy is the irritation of the mouth, tongue and pharynx which is so often *reported following*

its use. If careful attention is paid to technique, this complication may be avoided in all but a very small percentage of cases

Technique becomes more important in treating the patient with emphysema because the infection to be treated is deep in the small bronchi and bronchioli rather than in the trachea and large bronchi as is the case in bronchitis in otherwise normal individuals

The nebulizer must be capable of delivering an aerosol in which 50 per cent or more of the particles will have a diameter of approximately 2 5 μ. This is important to ensure the delivery of these particles as far into the bronchial tree as the inspired air will travel The small sized apparatus made to hold a few cc is preferable to those of larger size Whether or not there is an opening in the body of the nebulizer is unimportant There is neither virtue nor danger in the use of oxygen in this technique, so whichever source of gas under pressure is most easily available should be used A Y-tube is often used so that a patient, placing his thumb over the open end of the Y at the beginning of inspiration, may start the aerosol At the beginning of expiration or during cough, he removes his finger thus ending aerosolization and saving solution

This is effective when the coordination of patients is sufficiently good and their time reaction rapid It has been found in actual practice, especially with older patients, that such exact coordination is rarely present Furthermore, in emphysematous patients, inspiratory time, during which the aerosol is to be delivered, is quite short ranging from $1/8$ to $3/4$ second, and expiration takes much longer With an average time reaction of 0 75 seconds and with muscular confusion which frequently occurs, the majority of patients lose from $1/2$ to the entire time of inspiration before they place their thumbs on the Y-tubes The beginning of inspiration, the air that will penetrate deepest into the lung, is lost and the value of the aerosol considerably diminished

It seems in the emphysematous patient at least, that it is better to eliminate the Y-tube despite the obvious waste during expiration The mouth and the pharynx will be full of aerosol at the beginning of inspiration and perhaps deliver more to the small bronchi than would occur otherwise

If the nebulizer alone is used, it should be held just at the lips of the open mouth or slightly away from it. The lips should not be closed over the barrel of the apparatus because this interferes with deep inspiration and tends to encourage precipitation of the solution in the mouth and on the pharyngeal walls. There are, however, special apparatuses which aid in maintaining a high concentration of aerosol in the respiratory tract.

The most important of these are the nebulizer attached to a tube with a rebreathing bag described by Barach; the nebulizer inserted into a face mask and used with a demand valve (Barach), nebulizer with the face tent (Segal), and that associated with I P.P B Anyone of these apparatuses and techniques, properly used, are effective from the simple nebulizer alone down to the I P.P.B. machine. The highest concentration of nebulized particles is maintained in the tracheobronchial tree when the rebreathing apparatus of Barach is used

In most cases, bronchodilation should be used as well as the antibiotic material This is more effective if it precedes the antibiotic aerosol by 10 to 20 minutes than if both are mixed and used as one aerosol The flow should be regulated so that it takes about 8 minutes to nebulize 1 cc of solution. A more rapid flow is wasteful The patient should be instructed to breathe easily and to inhale as deeply as possible on each fourth or fifth inspiration This will avoid the fatigue commonly caused by the attempt to overbreathe When the solution has been used up, the same nebulizer should be filled with 2 to 3 cc. normal saline and this aerosol should now be inhaled. This will remove any of the antibiotic which has been deposited in the nebulizer and also aid in washing down any excess deposit in the larynx and trachea and also add more liquid to the bronchial contents. Following this, the mouth should be well washed out and the patient should drink a glass of some liquid in order to wash the back of the tongue and pharynx

This attention to detail may seem troublesome, but it is necessary to ensure the efficacy of the treatment and to avoid irritation of the mouth and pharynx This aerosol therapy, to be effec-

tive, must be continued for a long period and is thus more liable to complication

The minimum period of therapy should be six weeks During this time, the patient should take three treatments a day In many cases, it is desirable to continue treatment for a longer period changing the frequency to twice or even once a day

The antibiotic aerosol is always a liquid The various micropowders of antimicrobial drugs that may be inhaled as a dust have been found to be more irritating than efficacious In addition, adding liquid to the bronchial contents helps in eliminating this material and, by furnishing a high humidity in the inspired gas, is soothing to an irritated mucosa

Aerosol therapy can also accomplish liquefaction of bronchial contents or the addition of liquid as a vehicle in which the thicker mucus may be carried up to the trachea and expectorated

Normal saline in adequate amounts will frequently be an effective substance Where the material is particularly viscous, irritating and producing bronchospasm, detergent aerosol may increase the penetration of the liquid into the mucus Alevaire (Miller) has been used and more recently a detergent solution containing KI (Levine) When the mucus is liquid, its viscosity may be diminished by aerosol therapy However, if the mucus has become inspissated or is rubbery in consistency, it does not become liquid even when placed in a detergent solution overnight It is thus unreasonable to expect that the inhalation of an aerosol of such a detergent will liquefy this type of mucus

The effect of the aerosol here is to work the mucus loose from the bronchial mucosa, make it easier to move it up along the bronchial tree and eventually get it into a position where it can be coughed up, still in a relatively solid form

This type of aerosol may be administered by any of the apparatuses previously mentioned, using 3 to 5 cc for each treatment One can also use the larger type of nebulizer which produces a thicker "smoke" With these, the treatment period is ½ hour 4 times a day

This may be combined with antimicrobial therapy, as previ-

ously mentioned When this is done, it is better to use the antimicrobial drug in the manner described and to use the larger volume of liquid as aerosol at another time, not less than an hour later. When antimicrobials are used, retention is important When liquefaction is sought, the result is generally rapid expectoration

Another method of liquefaction of secretion is by enzyme aerosols These are undoubtedly effective, but complications of a serious nature are so likely to occur that it is best to use other, safer methods which are available for bronchial drainage.

The major reason for treating bronchopulmonary infection is to improve ventilation of the lung, since the infection in the majority of cases causes no toxicity and is not a problem of itself Bronchial drainage and a clear airway is therefore the goal As the infection is controlled and the secretion made more liquid, the patient will cough more and expectorate a large volume of sputum

It is, however, necessary to remember that this cough is very inefficient regardless of how productive it appears. Frequently the patient is expectorating only that material formed high in the bronchial tree leaving material in the small bronchi and bronchioli to remain where it is This latter area may not be affected to any great extent by aerosol therapy if partial or complete obstruction stops the continuing air current which carries the nebulized particles. Consequently, although aerosol therapy may be necessary for adequate bronchial drainage, adequate bronchial drainage is essential to the effectiveness of aerosol therapy. Both types of treatment must be administered simultaneously

There are two approaches to bronchial drainage applicable to aerosol therapy postural drainage and exsufflation Of these, exsufflation is the more important. This is because the secretion to be drained is in the smaller bronchi, is thick and adherent and thus is unlikely to move much by change of position Exsufflation, which creates an air flow of increased velocity, will move secretion along in the bronchial tree to a point where it may be easily coughed up by the patient

Experience with exsufflation suggests that this technique should be used in emphysema whether or not there seems to be material

in the bronchi The relative inelasticity of the lung is one factor which militates against an effective cough Others are the pressure of alveoli against bronchioli producing collapse and obliteration of the lumen, bronchospasm which may act as a barrier, and the rigidity of the chest cage itself In fact, observation of the emphysematous patient during a spasm of cough shows that, regardless of muscular effort and the fatigue produced, very little expulsive force is produced and very little actual result obtained

The mechanism of exsufflation is ideal in emphysema An initial insufflation under some positive pressure will inflate the lungs equally The importance of this cannot be overestimated These lungs do not inflate equally because the elasticity is uneven and because the bronchial lumina are more or less obstructed When the ingress of air does not depend upon the previous expansion of an area of lung, areas of imperfect expansion may for the first time receive an adequate amount of ventilation This means that air will now get beyond secretion which has been obstructing small bronchi

It is the air distal to the secretion that operates to remove it It is not a matter of pressure or of muscular force Once this air has been introduced behind the secretion, the next phase, that of exsufflation, has a chance to carry the material along the bronchi In the emphysematous patient, this may be aspirated mucus and foreign matter which has been retained in the fine bronchi for a period of years

This has actually been proven on a former foundry worker with silicosis Under exsufflation he expectorated black silica-containing material that was aspirated seven years previously and which had not been expectorated during the past five years Other patients have coughed sputum containing tiny thread-like casts of actually inspissated mucus Sometimes, very little is expectorated although the patient mentions a satisfying cough and the sensation of small amounts of material appearing in the pharynx to be swallowed

Postural drainage should be used as an adjunct to exsufflation and as part of the treatment of emphysema, rather than primarily a method of clearing the bronchi Once exsufflation has moved

material into larger bronchi, posture can be used to facilitate its further removal

Placing the patient in the head-down position as described by Barach should be used in all these cases, for improved drainage of the bronchi as well as improved excursion of the diaphragm

As a logical development of this idea, we have recently varied the head-down position by the use of an oscillating bed* designed to have a very slow cycle and to pause in the head-down position for predetermined periods of 5 to 30 seconds. This is kept running almost continuously, and particularly during the period when the patient is asleep The effective action is the same as the head-down position, using the weight of the abdominal organs to elevate the diaphragm. Oscillation seems to add excursion to the diaphragm, changes in blood return to the chest, preventing the secretion from settling anywhere in the bronchial tree, in addition to allowing the patient to use this treatment throughout the night and for whatever portion of the day is deemed desirable

It should be noted that this treatment is most rapidly effective when combined with aerosol therapy and exsufflation with negative pressure If the bronchi remain partially obstructed by spasm and secretion, the elevated diaphragm only causes pressure on the retained air and cannot rise as far as it should.

Eight patients have been treated on this oscillating bed at the Edgewater Hospital They were selected because they had these characteristics in common They were males over the age of fifty, with one exception He was a man of 30, with extensive bilateral fibrosis from an arrested far advanced tuberculosis of twelve years duration Each patient showed emphysema and fibrosis with evidence of diffuse bronchial obstruction In every case the diaphragm was depressed and immobile during the deepest respiratory effort

Two of these patients were placed on the bed with no other treatment than broad spectrum antibiotics given by mouth The bed was set in motion so that in one complete cycle, the feet would be lowered to a 12° angle and then the head lowered to 15° This was continuous during the night and during the day, interrupted

* J H Emerson Co , Cambridge, Mass.

for meals and certain rest periods The patients felt comfortable, breathed more easily, and slept well However, at the end of a week, the motion of the diaphragm had improved to an excursion of not more than one inch Subsequently, these and the other six patients received aerosol therapy and used the exsufflator for four periods each day The first noticeable change was that the patients no longer found it necessary to cough violently in the morning to eliminate secretions which had collected overnight Because of the continuous rocking motion of the bed, there had been steady elimination and no collection of material

At the end of one week, the patients reported that they were breathing more deeply and with greater ease. Their diaphragms were seen to have an excursion ranging from 2 to 3 inches What was probably more remarkable was the unconscious use of abdominal muscles in breathing This latter fact was taken advantage of by making the patients practice abdominal and manual exercise while lying on the bed

The treatment period of this Edgewater bed ranged from 10 days to two weeks Increases in vital capacity ranged from 700 cc to 1600 cc The maximal breathing capacity showed improvement with increases ranging from 10 liters in one of the older and weaker patients to a 42-liter increase in a more vigorous man The most remarkable change was seen in the ease of breathing This was best demonstrated in the improvement in ability to exercise Patients who had been dyspneic when walking on the level, now were able to walk up and down two flights of stairs without serious dyspnea

In reviewing these cases, it is apparent that more than one approach is necessary in treatment Aerosol therapy furnished bronchodilatation, antimicrobial effect and adding of liquid to bronchial contents Exsufflation with negative pressure added the all-important factor of mobilizing and moving up the secretion present deep in the bronchial tree Postural drainage in the head down position, improved by the cycling bed, prevented collection of secretion, aided in drainage, and stimulated function of the diaphragm

Therapy of the bronchial infection in the emphysematous pa-

tient must be part of the total treatment, synchronized with it and designed to accomplish the same ends. Its essential parts are aerosol therapy, exsufflation with negative pressure and postural drainage

These three should always be used together. There is no case in which a better result will be obtained by *eliminating one and there* is no danger in the use of any one of these in any patient

A theoretical objection has been raised that the pressure changes of exsufflation might be contraindicated in patients with emphysematous blebs or in individuals with cor pulmonale. This has not been borne out in our experience

Patients with blebs demonstrable on body-section roentgenograms have been treated and no untoward incident occurred None need be anticipated Since the blowing phase of this treatment is simultaneous with inspiration, the actual pressure is either atmospheric or a few centimeters of water above it During the negative expiratory phase, the actual pressure is not very great since the air is rushing out at a high velocity and the time *of expiration is not long enough to evacuate all the supplemental* air Even if all of the pressure for which the machine is set were *applied to the bronchial tree, there should be no trouble* The pressures of 40 mm Hg exerted for 1½ to 2 seconds at the mouth would probably be greatly diminished by the time *they reached* the alveoli and it is well to remember that the average cough exceeds this pressure and a severe cough may create a pressure three to four times as high

The same has been true for cases of definite cor pulmonale. There has been no sign of increased pulmonary arterial pressure or embarrassment of the right ventricle. Experience has shown quite the opposite effect This is best demonstrated [illegible] he studies on an emphysematous m [illegible] before treat [illegible] s very dyspneic His ulmonary [illegible] ssure was 3 [illegible] t and 48/20 with [illegible] l exer [illegible] diac outp [illegible] liters at rest and [illegible] o 9 0 [illegible] rtion. Af [illegible] ted, including ex [illegible] vith [illegible] ure fou [illegible] r a period of t [illegible] he [illegible] ated. was no long [illegible] on [illegible] ion.

artery pressure was 26/9 at rest and increased with the same exercise to 36/18 The cardiac output was 3 89 liters at rest and increased to 6 7 with exercise It is interesting to note that his resting oxygen consumption changed from 394 cc /min before treatment to 280 cc /min afterward These figures indicate that the work of the heart was actually eased by the therapy and that the work of breathing was considerably diminished

It can properly be said, therefore, that any patient who can cough without noticeable damage to his lung or excess strain on his heart may be safely treated by the combined therapy, including exsufflation

The treatment of bronchopulmonary infection in the patient with emphysema should begin with a bronchodilator aerosol On the same day, following this by 10 to 20 minutes, an antibiotic aerosol can be started Antimicrobial and bronchodilating drugs may also be given orally at this time if the indication exists

From this point, treatment will be varied by the needs of the individual patient If there is a large amount of fairly thin expectoration, exsufflation should be started immediately and continued until less material is formed If, however, there is very little obvious secretion, the aerosol therapy should be given for several days before exsufflation is started In these cases, it is advisable to add an aerosol of normal saline or of a detergent solution to add liquid to the bronchial tree

After three or four days, exsufflation should be started, whether or not expectoration has begun It is in these cases that long retained inspissated material begins to appear on the second or third day of the use of the exsufflator The expectoration of this material is greatly aided by using 3 to 5 cc of saline or a detergent solution aerosol, 15 minutes to one-half hour before using the exsufflator

When the bronchial secretion is thick and viscous, as indicated by rhonchi heard in the chest and the obvious difficulty of cough and expectoration, an attempt should be made to liquefy it Potassium iodide by mouth should be used whenever possible As a direct approach, 3 to 5 cc of normal saline or Alevaire should be inhaled as an aerosol four times a day The use of a solution

containing tergitol 0 125 per cent and potassium iodide 0 1 per cent has recently been found to be less irritating and more effective than other aerosols Whatever else is being done for the patient, this aerosol should be continued as long as there is any evidence of thick, sticky bronchial secretion

In this type of patient, exsufflation should be started immediately, although for the first few days it will be difficult to determine that any direct benefit is being derived since this type of mucus is most difficult to eliminate in any patient With the rest of the picture of emphysema, it is certain that bronchospasm, edema, bronchial collapse and complete obstruction are all present at one time or another Consequently, cough will not only be inefficient, but will produce irritation, pressure, bronchiolar collapse and may result in further lung damage Cough must be kept to a minimum while drainage is accomplished at a maximum rate

Exsufflation is established, following the aerosol treatment by about one-half hour Sometimes, in particularly thick secretion, aerosol with saline or detergent solution should also follow exsufflation

Drainage should be aided by placing the patient in the head-down position Although in simple bronchiectasis and bronchial infection with other types of pulmonary pathologic conditions, drainage is to be done in the position which produces most cough and expectoration, drainage in the emphysematous patient should always be with the patient in the head-down position

There are two reasons for this First, the areas of faulty ventilation, spasm and most retention are at the bases of the lung, and these are the areas to be drained. Secondly, the head-down position is a valuable method of regaining diaphragmatic function. When this is accomplished, the drainage of the bronchi in the base of the lung is very much more efficiently carried out

The patient should be placed in this position only after there has been some bronchodilatation and after some of the obstructing secretion is in a position to be removed If this is done before the bronchi are open and drainage is possible, the diaphragm cannot rise as desired and the patient may become uncomfortable If the

bronchi are reasonably clear, the head-down position become that in which the patient can both breathe and expectorate with greater ease

Even when infection has been eliminated from the bronchial tree, the problem is not yet eliminated For the emphysematous patient is prone to recurrent bronchopulmonary infections These should be treated early, rapidly and vigorously by the customary methods of handling such acute infections If this is done there will be no need for establishing this long complicated program But if the infection is allowed to become well established, it may be necessary to return to the combined program for the period indicated by the condition of the patient

A selective bibliography is given on page 234

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Chapter 9

THE MECHANICS OF BREATHING

HOWARD G DAYMAN, MD

THE VENTILATORY MECHANISM

It is convenient to introduce this subject with a brief description of salient steps in the evolution of the breathing mechanism This aspect of our development leaves little room for conjecture Usually the problems are clear, the mechanical principles simple, and the solutions few Ventilatory disorders in man often highlight these principles and exemplify shortcomings in adaptive design

When vertebrates emerged on land an internal respiratory system became necessary to conserve water during gas exchange with air A saccular outgrowth of the gut, the primitive lung occupied a dorsal position in the thoraco-abdominal space It was ventilated by means of intermittent positive pressure through alternate distention and contraction of the buccal cavity In aquatic forms the ribs had been simple extensions from the transverse processes which gave form and strength to the body On land, the more cephalic thoracic ribs were required to contribute anchorage for a weight bearing pectoral girdle and became short, sturdy structures capable of limited rotation about an axis lying at right angles to the axis of the spine, thereby insuring great mechanical advantage at the loss of ventilatory function Progressing caudally, the lower ribs exhibited axes of rotation more and more acute with that of the spine, permitting the costal arch to open like calipers with some upward displacement of the anterior ends (Fig 9 1) This general design, a prototype for all subsequent vertebrate thoraces, permitted passive expansion but, lacking a

respiratory movement of the chest and belly tends to be antagonistic

To withstand the higher ambient pressure, the diaphragm must be arched with convexity toward the lung; it can pull but cannot push Moreover, this design admirably serves to integrate its function with ribs and belly wall The same relationships obtain in all mammals including man, but are easiest to study in fleet footed quadrupeds having numerous free ribs on which the spinal hinges impose a lateral inspiratory movement. The edge of the long diaphragm attaches to the anterior ends of these ribs and most of its high arc faces dorsally rather than cephalically. The abdomen lies within the embrace of the thorax and each costal segments demarks a functional mechanical unit (Fig 9 1) In man there are only five free ribs, of which number 8 can be considered representative The erect posture of man imposes a downward slope to counterpoise the added vector of gravitational force Employing geometric figures these relationships can be projected in a single plane without introducing serious mechanical distortion (Fig 9 2) During inspiration diaphragmatic traction assists in everting the rib up to a point where the direction of pull lies medial to the radius of rotation Further inspiratory movement of the diaphragm then restricts lower thoracic expansion. This normal sequence can be demonstrated by sensitive recording of costal movement when there is no other ventilatory impediment than paralysis of one diaphragmatic leaf (Fig 9 3)

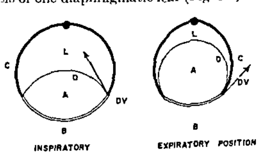

FIG 9 2 The mechanical relationships of functional respiratory unit.
A Subdiaphragmatic space. B Belly wall C Costal arch D. Diaphragmatic arch. L Lung space DV Vector derived by direct traction of diaphragm on costal margin.

It can be seen in Figure 9 2, that the design permits great flexibility in ventilation For abdominal breathing alternate contraction of diaphragm and belly wall can ventilate lungs without thoracic participation other than anchorage, and without altering static subdiaphragmatic pressure Considering the inspiratory position in Figure 9 2, and assuming a constant pressure in the thorax, subdiaphragmatic pressure can be elevated by simultaneous contraction of the diaphragm and belly wall which necessarily makes the enclosed space circular This is readily demonstrated in a trained subject by a drawing in of the lateral costal margin Shape must conform to pressure

It can also be elevated without contraction of the diaphragm or belly wall but contingent on passive tension of these elements, the structures to which they are attached, or on which they abut Four methods are used head down position, employing the force

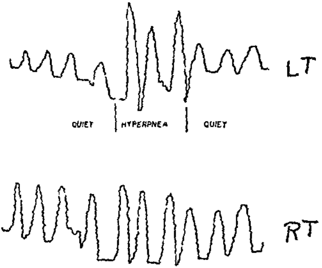

Fig 9 3 Effect of diaphragmatic traction on costal movement
Smoked drum recordings of the movement of wands held with constant pressure against the anterolateral aspects of the ribs number 8 The left diaphragmatic leaf is paralyzed Respiratory participation of the intact right leaf assists rib movement in quiet breathing, restricts it in deep breathing

of gravity, the instillation of a gas into the peritoneal space, the contraction of *lower* abdominal muscles; and the pressure of a *lower* abdominal belt The resulting increment of subdiaphragmatic pressure is small, often less than 10 per cent of that attainable by expiratory muscular effort, but *with each of the above* methods there is an associated increase of subdiaphragmatic volume to fill any space vacated by upward displacement of the diaphragm or expansile displacement of the lower chest wall. These changes improve the integration and efficiency of costodiaphragmatic function

The nature of the mechanical changes in emphysema and the subjective response to therapeutic use of the above methods, often without volumetric evidence to explain it, strongly suggests that economy in the work of breathing is an important therapeutic aim. In the untutored patient, expiration can evoke the most violent muscular effort of which the human body is capable Breathing produces dyspnea Thoraco-abdominal pressures reach an extreme range Assuming a cross section area of 400 sq cm, and pressure of +110 mm Hg, the upward thrust of the abdominal contents against the lung bases amounts to 125 lb for every expiratory effort

By contrast, subdiaphragmatic pressure in health is nicely adjusted close to ambient pressure except during forced expiration It is readily measured in patients receiving therapeutic pneumoperitoneum A sharp sniff causes checkvalve narrowing of the nares and thoracic pressure drops to −40 mm Hg or lower, yet a shift in abdominal pressure is scarcely detectable With a sharp expiratory effort, especially if the glottis is initially narrowed ("Clear your throat gently please"), abrupt rise in pressure reliably indicates that the exploring needle communicates freely with a gas containing intra-abdominal space (Fig 9 4).

During quiet breathing, in health, abdominal pressures often rise about 1 cm with inspiration The same is true during quiet breathing in emphysema, but if it becomes at all labored one observes first a dicrotic pressure wave then a dominant sustained expiratory rise of pressure In advanced disease tactile sense of

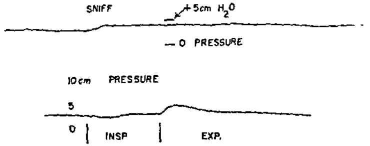

FIG 9.4 Upper abdominal pressure

Upper abdominal pressure in a supine tuberculous patient under treatment with pneumoperitoneum of moderate size which elevates the general level of pressure by about 4 cm H_2O above normal Sniff, slow inspiration, sharp expiration recorded

In the main, subdiaphragmatic pressure is held quite constant except (1) During expiratory effort in the presence of respiratory obstruction (2) During strenuous exertion when the glottis is closed and high thoraco-abdominal pressure contributes rigidity to the trunk (3) During similar efforts or straining at stool, etc, when the glottis may remain open and elevation of pressure is thus confined to the abdomen alone

the examiner suffices without cavil The belly wall is boardlike. The examining finger placed in vagina or rectum is firmly compressed during expiration

Advanced cases also manifest a pronounced inspiratory handicap due to thoraco-abdominal antagonism. The diaphragm is not only flat, fluoroscopy regularly shows that one or more quadrants are inverted These areas become even more inverted on forced expiration and move paradoxically upward on sniffing With all forms of breathing, the diaphragm constricts the circumference of the lower thorax during inspiration (Fig. 9.5)

Meanwhile powerful accessory muscles of respiration acting through the upper ribs which have great mechanical leverage can violently agitate the thoracic cage in a reciprocating cephalocaudal direction, creating for the unwary clinician the entirely falacious impression of hyperventilation Moreover, the abdomen is obliged to follow this movement by alternate paradoxical collapse and protrusion The events on inspiration are cephalic thoracic move-

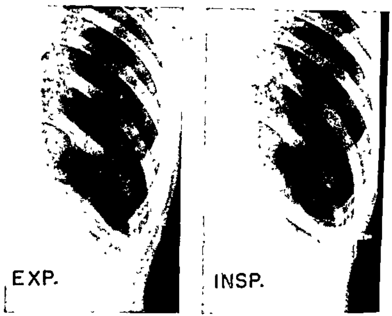

FIG 9 5 Left posterior quadrant of diaphragm in a patient with advanced anatomic emphysema Small pneumoperitoneum space present

ment, constriction of lower thorax, collapse of the abdomen On expiration, the sternum moves caudally, the lower thorax expands, and the abdomen protrudes A similar phenomenon occurs in chronic poliomyelitis with total respiratory paralysis except for neck mucles Here the soft demineralized lower ribs, unsupported by muscle, cave in because of higher ambient pressure instead of diaphragmatic pull Both situations exemplify the disastrous effect of incomplete pulmonary enclosure in negative pressure breathing vertebrates

Should an emphysematous patient be instructed to synchronize the movements of the upper thorax and abdomen, the lower thorax becomes further constricted on inspiration, a dubious advantage Frequently, this vicious circle cannot be interrupted but there are occasions when the above mentioned principle of upper abdominal filling can be applied, with immediate cessation of thoraco-abdominal antagonism The slight elevation in pressure itself could hardly account for this change

STATIC ASPECTS OF LUNG DISTENTION

At birth the lungs begin to inflate Thereafter no physical process, acting inside or outside the body, can again render them totally airless, with the notable exception of atelectasis because of the combined effect of blocked airways and absorption of all vestiges of air by an intact circulation Pressure is required to inflate the lungs Assuming a state of postnatal atelectasis, high pressure is first required to disrupt adhesion between apposed bronchial walls. During open thoracotomy, pressure of 30 mm. Hg or more may be necessary to initiate inflation Thereafter a lower pressure suffices to cause air flow and to overcome the viscosity of tissue deformation, but when inflation reaches the zone of the expiratory reserve volume, the lung is placed under tension, called Lung Tension This is a static factor, and is here expressed as pressure,

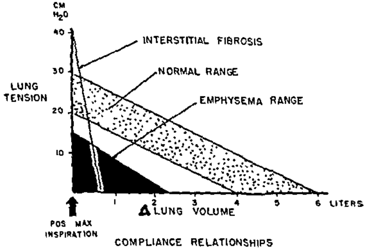

FIG 9 6 Lung Tension/lung volume relationships—compliance
General range is shown The actual curves in health and in interstitial fibrosis are essentially straight Those in emphysema show various sigmoid variations See references for origin of data Lung volume, the abscissa, refers to the volume exhaled from a position of maximum inspiration, the only feasible common point of reference in view of uncertainties about measurement of total capacity in emphysema

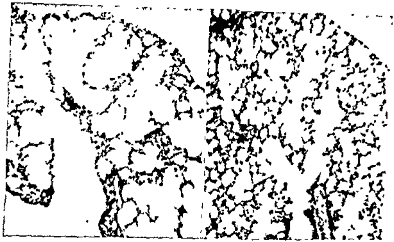

FIG 9 8 Alveolar mechanics—lung structure at inspiration (left) and expiration (right) in mouse lung (same magnification)

Mouse lung, being small, epitomizes the structural changes in a single radial section Prepared by the method of Yegian, the trachea of a skinned mouse was obstructed at the desired respiratory phase Then the animal was quickly dispatched and the entire carcass fixed with organs *in situ* On expiration the alveolar space is hemispheric. Distention of the lung broadens the mouth of the alveolus but the dome cannot distend radially since it lies back to back with other alveoli under the same stress. Only as the dome flattens can its elastic elements come under direct tension The distending unit, whether alveolar duct or sac, thus has an accessory system of recoil which comes into play more and more as the unit inflates.

alveolar volume decreases on inspiration As alveolar shape changes from that of a cup to that of a saucer, elastic elements across the dome come under more and more direct stress Were it the intent to construct a system out of perfectly elastic material wherein volume would parallel pressure, this admirable design would have to be employed in one modification or another

To distend the lung so that all segments under static conditions retain the proper amount of air, Lung Tension must increase equally in all segments to which air is apportioned This, together with the dynamic aspect of equal resistance to air flow in the airways, constitute the two factors governing distribution of air The static factor may be applied more generally by stating that a unit change

in volume, for a unit amount of normal lung, gives a unit change in Lung Tension. Although the volume required to elicit a given tension is necessarily small for animals the size of a guinea pig, the range of Lung Tension is the same as that for man. Similarly, in patients with severe chronic respiratory paralysis, the volume of air which must be mechanically insufflated to produce a given Lung Tension varies directly with the height of the patient and inversely with the amount of atelectasis To produce a given tension, the volume needed for one lung is half that required for two lungs In the case of interstitial fibrosis, Case R S (Fig 9 6), a unit increment of volume produced seven times the normal increment of tension, reaching 40 cm H_2O at a position of maximum inspiration, a dangerous transpulmonary pressure close to that which will regularly rupture mammalian pleura Fibrosis must have been universal and continuous The patient died of bilateral spontaneous pneumothorax Conglomerate silicosis exemplifies discontinuous fibrosis which imposes undue inspiratory strain on intervening parenchyma leading to anatomic emphysema, mechanically the reverse of Case R S

The separate effects of static and dynamic factors are illustrated in Case E F (Fig 9 9) This is an example of local obstructive emphysema with intact parenchyma The mechanical principles set forth in the legend can be applied to elicit signs of local bronchial obstruction in tumor, inflammation or foreign body. Local *anatomic* emphysema, by contrast, is exemplified in the emphysematous bulla These familiar excrescenses are obvious near the apices of emphysematous lungs At the bases they more clearly illustrate the transition from normal parenchyma but are readily overlooked in deflated lung They protrude on inflation and often, being multiple, deep clefts intervene between them These clefts in silhouette constitute the so called "diaphragmatic tents" on the roentgenogram The space inside the bulla is traversed by a lacy network of parenchymal fragments and threadlike vascular remnants Colored gelatin instilled through the bronchial tributary finds a tortuous channel through fragmented parenchyma into the space There is no direct bronchial communication Figure 9 10

showed suspicious minute scattered areas of rupture rather than large torn apertures, and overall Lung Tension was not decreased. In tuberculous guinea pigs the noncompliant foci of disease impose additional strain on neighboring healthy parenchyma and obvious tearing results, especially between two adjacent lesions. If a linear elastic system is severed in one place counter-tension is impossible Two and three dimensional systems are less vulnerable In such a system there is packing of parenchyma about the periphery of the tear which offers some protection. The eversion of tissue surrounding the bulla (Fig. 9 10) is an example. It can also be demonstrated microscopically in acute experiments.

The facts remain that severe parenchymal tearing does reduce Lung Tension, many small tears properly distributed throughout the parenchyma should reduce it, and in human emphysema reduced tension is associated with demonstrable parenchymal dehiscence Loss of Lung Tension is a result, not a cause of anatomic emphysema The precise relationship to volume is not clear because total capacity measurement by gas dilution methods cannot sense the numerous areas which are poorly ventilating or non-ventilating In spite of this, there is no question that in anatomic emphysema the lungs do not come under tension until a volume much larger than normal is insufflated. This feature indicates that elements of the normal system have been torn from their moorings There being no stress upon remaining elements no counter-tension is exerted, and "loss of elasticity" is not to be inferred

The small range of volume over which emphysematous lungs do exert tension, often within one liter of maximum inflation, is characterized by a variable Compliance pattern In some cases tension rises sharply (low Compliance) followed by a plateau (high compliance), not unlike the pattern for a rubber balloon Considering the many factors affecting tension/volume relationship this is to be expected, and the slope of the curve in any event is not a measure of "elasticity" for the structures under stress

When fully inflated the tension of emphysematous lungs is lower than normal, often below 10 cm H_2O pressure This property can be attributed to loss of parenchyma rather than loss of elas-

ticity In such case the disparity between Lung Tensions at position of maximum inspiration in health and in emphysema should reflect the departure from normal architecture This may be a useful indicator for evaluating anatomic emphysema

One aspect of Compliance deserves separate comment If resistance to air flow varies from segment to segment, equilibration of pressure within the lung may not be possible in the time allowed for apnea when static pressures can be measured The less time allowed, the greater the disparity of Lung Tension between segments This means that unobstructed segments will be overventilated and impose a wider fluctuation on static pleural or esophageal pressures than would be the case if air were evenly distributed This reduces the numerical value for Compliance (See Figure 9 12 for method of measuring compliance) A test for uneven distribution of air has been devised by Mead, employing this principle In health, the width and streamlining of airways nicely apportions the air to all segments and Compliance remains relatively constant regardless of the frequency of breathing If distribution is uneven Compliance decreases as the frequency increases Actually, uneven distribution is the rule rather than the exception in pulmonary disease

To appreciate fully the relation between structure and function one must study serial sections of lung fixed in inflation In emph sema the distending components distal to the bronchioles lac identifying features and are converted to intercommunicatin polyhedral spaces of varying size, some of them enormous Alveolar partitions which serrate the circumference of normal distending units are notably few or absent in affected areas Figure 9 11 shows several examples with normal architecture for comparison It should be emphasized that lung fixed in inflation presents a microscopic appearance strikingly different from that of the usual preparation The alveolar sacs and ducts of normal lung can be clearly seen with the unaided eye In advanced anatomic emphysema the diameter of the spaces may be greater than the width of the usual microscopic slide They bear no resemblance whatsoever to alveoli, hence we refer to them simply as terminal air spaces

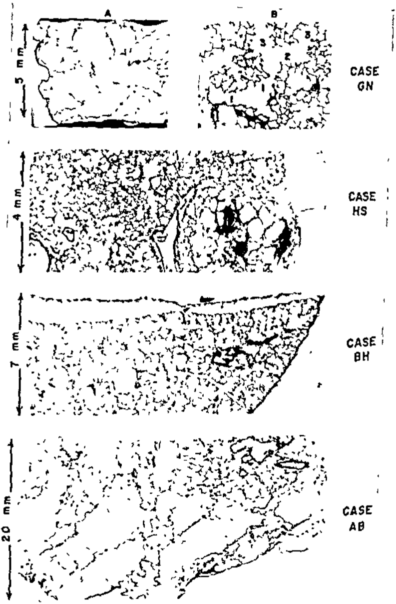

FIG. 9 11

DYNAMIC ASPECTS

Previous sections dealt with the mechanics of the musculoskeletal bellows, the static response of lung, and in general the respiratory application of Pascal's principle Ultimate resultant of these actions and indirectly of the neural and humoral factors which govern them, is volume rate of air flow, symbol $\dot{V}$, or in some of the illustrations *Fl* Flow is distinct from linear velocity, miles per hour We have been prone to regard ventilation as relatively effortless, and so it is for *quiet* breathing in health But to achieve high rates of flow, or to surmount obstruction, the human body whether healthy or diseased may have to bend every effort to the purpose of breathing The dynamic aspects of flow itself can exact the greatest expenditure of energy

To cause ventilatory air flow, ambient pressure must differ from pulmonary pressure (PuPr) the pressure in the terminal air spaces

FIG 9 11 Lung structure (*Scale shows actual size*)

Case G N (A) *Diffuse uniform breakdown found in much of left upper lobe* Normal parenchymal components could not be identified in 200 serial sections Lung Tension for this segment very low, Compliance curve unknown

(B) *Normal architecture present in left lower lobe of same lung* Included in illustration are first and second order respiratory bronchioles, alveolar ducts and sacs *Left upper corner shows some fragmentation which occured during preparation Inflated lung tissue is so delicate that technical artifacts are always* present, hence serial sections are needed to help identify them, as well as to provide *the basis for three dimensional evaluation* Two hundred serial sections prepared *from this block* This excised lobe had a *normal Compliance* Lung TENSION was carried to 28 cm of water pressure without rupture of the pleura

Both specimens were inflated with fixative at same pressure Magnification same for both

Case H S There are numerous scars with perifocal emphysema, a late result *of widespread dispersion of contaminated blood from a tuberculous cavity* Clinically breathing was nonobstructive *Normal Compliance retained in excised* specimen Maximum tension 24 cm H_2O

Case B H Focal emphysema, Normal architecture in many areas Death *from other cause* Lung Tension probably somewhat reduced *Compliance pattern unknown*

Case A B *Representative area in severe, widespread anatomic emphysema,* maximum Lung Tension 2 cm H_2O pressure *Extremely fragile, note wrinkling of tenuous walls and pleura* (right lower corner).

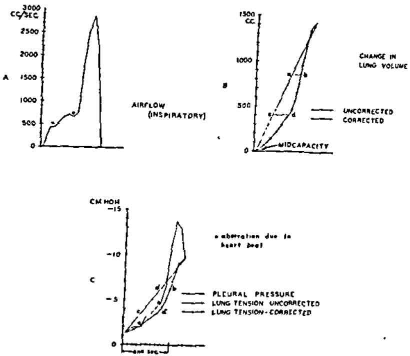

FIG 9 12 Dynamic pressures in ventilation

An erratic inspiration in a healthy subject was selected to emphasize variability Air flow and dynamic pleural pressures were recorded by an optical method previously reported The breath began at rates of flow encountered in quiet breathing, then suddenly increased to nearly three liters per second Increments of volume were plotted from the air flow tracing at $1/10$ second intervals *Total volume of the breath was 1430 cc For this change in volume there* was 8 2 cm change in pressure, giving Compliance of 0 17 l per cm H_2O pressure A series of breaths on this patient confirmed this value and the rectilinear nature of Compliance Successive increments of volume could then be integrated, and since air flow was erratic, the corrected curve for volume departed considerably from that derived by assuming air flow to be uniform A similar curve was derived for LT by integrating successive increments; time correction a–b equals a′–b′ and c–d equals c′–d′ Since LT acts in the opposite direction to PlPr, LT bears a + sign in the equation, PuPr = LT + PlPr The values at b′ are −5 cm PuPr for inspiratory flow rate of 2530 cc /sec, giving 1 97 cm pressure per L/sec as the numerical value for resistance to flow

During expiratory flow calculations are the same except that PuPr is positive, *i e*, above ambient.

It equals the algebraic sum of Lung Tension and pleural pressure, PlPr

$$PuPr = LT + PlPr$$

Only during apnea, such as the static interphase between breaths, when pulmonary pressure is zero, does the numerical value for pleural pressure express the equal and opposite reaction to Lung Tension

Figure 9 12 illustrates the calculations and emphasizes the vast difference between dynamic and static pressures The reader will note obvious limitations in the method At low rates of flow, pressures are so small that even heart beat causes aberration No single value for pressure can be completely valid in a complex dynamic system It is a generalization at best

Finally, the method disregards viscosity which must play some part although necessarily a small one in emphysema Parenchyma in this disease is extremely delicate, and there is literally less of it (Fig 9 11) It cannot be handled without special precautions to prevent deformation Laennec dried the emphysematous lung before sectioning it Filling with warm gelatin followed by chilling helps to maintain structural integrity under the knife Even then it presents one of the most vexing problems confronting the microtomist

The viscous resistance to deformation, gram for gram, is unknown but response to gross handling and the morphology will convince the most critical observer that overall viscosity is categorically lower than normal, and most certainly viscosity cannot account for the fact that high dynamic resistance is confined to *expiration* in advanced uncomplicated anatomic emphysema By contrast the tissue in universal interstitial fibrosis might be expected to offer high viscous resistance The airways are capacious, expiratory rate of flow is high High Lung Tension would be anticipated and is demonstrable, Cases R S and A C, (Fig 9 21) But inspiratory flow rate is usually good enough to be in accord with the high Lung Tension Even in interstitial fibrosis the evidence does not clearly incriminate viscosity

Regardless of the state of health, *certain aspects of resistance suggest a cause quite different from viscosity.* Inspiratory resistance is uniform over a wide range of flow rate. Under like clinical conditions in the same subject expiratory resistance is higher, and it increases as lungs deflate Curves relating pulmonary pressure to flow, *tend to be straight lines on inspiration and loops on expiration*, (Figs. 9 13 and 9.14)

At the inception of a breath there is a brief period when resistance is low It is most conspicuous on expiration where it invites the conclusion that acceleration of pulmonary pressure causes *first a lower resistance, then an elevation above the general range* The shift is more pronounced the more rapid the acceleration particularly in advanced anatomic emphysema This phenomenon is a necessary sequel to the *expiratory checkvalve mechanism.* Flow

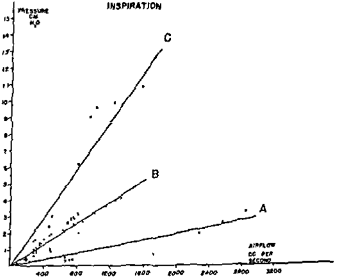

FIG 9 13 Inspiratory resistance

During inspiration pulmonary pressure retains a linear relation to air flow throughout a wide range of rate *Line A is that of a large man, Case T. M*, with normally functioning lungs B is that of a small woman in health C is that of a man with bronchitis and advanced anatomic emphysema Calculations are *based on data reported in 1951 Line B is plotted from* the composite points of four breaths The others are single breaths

is momentarily augmented by dead-space air extruded from major intrathoracic airways on expiration, and returned on inspiration as the airways open This mechanism has been repeatedly observed and meticulously described for nearly a century, but until 1951 it was consistently misinterpreted under the formerly prevalent belief that expiration must be "passive"

Even in quiet breathing there is a change of airway diameter during acceleration of flow, due to the factors of bronchial tension (BrT), and canalicular pressure (CPr) It is often detectable in the resistance curves although difficult to sense by direct inspection of the large airways Airway diameter varies according to

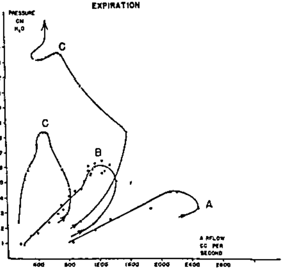

FIG 9 14 Expiratory resistance

These are the corresponding expiratory curves for patients listed in the previous illustration Each curve represents one breath The sequence of points is indicated by the direction of the arrows Points were determined at $^1/_{10}$ sec intervals during the course of the breath. Therefore the acceleration or deceleration of pressure or air flow can be gauged by the distance between points and the slope of the line at that range Observe that in advanced anatomic emphysema, increased expiratory pressure only enhances flow during the initial phase preceding checkvalve closure Thereafter flow is confined to low rates regardless of pressure Resistance is infinite except for leakage flow

the following relationship:

$$\text{Airway diameter} = f \frac{1}{\text{BrT} - \text{CPr} + (\text{PuPr} - \text{LT})}$$

But·

$$\text{PlPr} = \text{PuPr} - \text{LT}$$

Therefore

$$\text{Diameter} = f \frac{1}{\text{BrT} - \text{CPr} + \text{PlPr}}$$

As a corollary, extrinsic pressure acting on the airway (peribronchial interstitial pressure) equals PlPr. During apnea, BrT equals LT

During acceleration of inspiratory flow the airways widen and the caliber tends to be maintained by enhanced Lung Tension Similarly, expiration is initiated with concurrent narrowing of the airways which tends to be maintained as Lung Tension is decreased Airway diameter is not just a static phenomenon, it is predominantly related to the dynamics of flow.

So instructive and readily discernable is this aspect of the checkvalve mechanism that the student of chest disease can profit by personal observation in one or more of the following experiments on tracheobronchial dynamics.

Fluoroscopic Study

Select a slender subject who presents a clearcut fluoroscopic silhouette of the major airways, and can perform the breathing maneuvers listed below Fluoroscope the subject standing, with the left anterior aspect of the chest toward the screen Other projections can be added Have the subject make a sustained powerful effort to exhale against a closed glottis and note that the cervical trachea bulges slightly, but the intrathoracic airways do not Have the subject make the same effort but suddenly open the glottis to establish flow and note that checkvalve narrowing is momentary and occurs *immediately after* the glottis opens Request complete expiration at gentle pressure to differ-

entiate between checkvalve narrowing and the effect of depleted Lung Tension Have the subject cough forcefully and gently, in alternation, to relate checkvalve narrowing to dynamic intrathoracic pressure Measure the maximum pressure by the Valsalva technique Ask the subject to employ a panting hyperpnea emphasizing rapid acceleration of expiratory effort Note that check valve narrowing is less marked Outflow of air through the open glottis precludes the higher pressures attainable in cough, which is begun with the glottis closed

Bronchial Dynamics in the Excised Specimen

At necropsy remove thoracic organs without perforating the visceral pleura Strip off esophagus and aorta, and remove nodes if they obscure the posterior tracheobronchial membrane Remove the heart by cutting pulmonary artery and veins Tie into the trachea the largest cannula that will fit Suspend the lungs partly from the trachea, partly by floating in a pan of water, and if necessary employ soft cord to suspend gently the apices of upper lobes Keep pleural surfaces wet as much as possible Attach the tracheal cannula to a pumping device which can deliver high flow rates at pressures up to +30 cm H_2O on inspiration and −100 mm Hg on expiration Hand bellows, vacuum cleaner pumps, and synthetic coughing devices are readily adapted The system must be valved to permit sudden shift from inspiratory to expiratory pressures Observe that for healthy lungs sudden application of high expiratory pressure (−80 to −100 mm Hg) can cause tracheobranchial checkvalve collapse at any lung volume Moderate pressure applied when such lungs are full first causes rapid deflation and then checkvalve closure If expiratory pressure is initially applied when the same lungs are only partly inflated, closure is immediate If the lungs are severely emphysematous, checkvalve effect is immediately observed regardless of pressure or the stage of inflation at which it is applied

Study of the excised specimen establishes the fact that intrathoracic airways are, indeed, expiratory checkvalves, and that the mechanism operates independently of neural and humoral influences At the same time it is apparent that parenchymal changes

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do affect it even in the lifeless specimen. The relation between lung volume and checkvalve closure which prevails in health, but not in emphysema, is attributable to the influence of Lung Tension on bronchiolar pressure gradients.

When air flows through a tube or tubular system there is a decline of pressure downstream. As employed here, downstream always designates the direction in which a column of air is moving The rate of decline or gradient of pressure varies directly with rate of flow and with resistance to flow. Figure 9 15A illustrates these principles in a tubular system.

If pressure at entrance to the tube is common to a space enclosing the system (Fig 9 15B), the tube is compressed by a force proportional to the gradient and to the distance downstream At a given point compression equals the difference between canalicular pressure within the tube and that of the enclosing space Compression varies with rate of flow, when other conditions are constant Resistance (R) causes more compression downstream but less upstream conforming to reduced air flow. Resistance located at exit from the system minimizes compression upon the enclosed portion To this end, emphysematous patients purse the lips (or more frequently the larynx) during expiration

Resistance located upstream at entrance to the system makes the enclosed tube most vulnerable to compression and if the walls cannot withstand the stress the tube collapses, cutting off flow. All checkvalves embody the above principles. The rubber valve from a conventional basal metabolism tester is a typical example

Intrathoracic airways are potentially checkvalves on expiration. They branch ultimately into a multitude of terminal spaces which can be considered an entity, a terminal air space enclosing the tubular system Serious closure is averted by a number of circumstances of which two are outstanding. Structure and location equips the bronchioles to regulate pressure gradients for the entire respiratory tract The muscular walls are delicate; teased free of surrounding parenchyma, bronchioles can be crushed by less than 1 cm of water pressure, but situated upstream where compression is slight they can be supported against checkvalve collapse by adequate Lung Tension

In the previous section we observed the parellelism between bronchiolar diameter, Lung Tension, and lung volume (Figs 9.6 to 9.8) If Lung Tension is physiologically depleted by exhalation or is lost through anatomic emphysema, bronchioles thus unsupported should collapse under slight compression In such case all downstream airways, to a point where the trachea emerges into

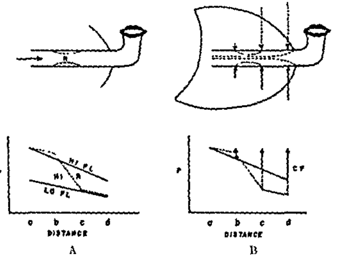

FIG 9.15A Flow through a tube

Direction of flow is a to d The graph depicts a small gradient during low rate of flow LoFl To double the flow, pressures at every point along the tube must likewise be doubled, HiFl This doubles the gradient If conditions of HiFl are otherwise unchanged but intrinsic obstruction interposed at R offers resistance of such magnitude as to reduce flow by half, the gradients are indicated by the dotted line, HiR LoFl gradients then prevail in unobstructed segments a-b and c-d The gradient b-c is higher That for the total distance, a-d, is three times that of LoFl, but the volume rate of flow for conditions of HiR and LoFl are the same

FIG 9.15B The enclosed tube

Pressure at entrance to a tube and common to a space surrounding it exerts compression on the tube proportional to the length of the arrows. Conditions of high flow (HiFl) give high compression solid arrows at b, c, d Resistance interposed at R reduces compression upstream and increases it downstream dotted curve and dotted arrows Checkvalve closure results when the tube cannot withstand the compression dotted outline

the neck would be subjected to crushing by the full force of intrathoracic pressures, which could thereby extrude dead space air (bronchial milking) but could not deflate the parenchyma except through leakage flow Greater expiratory effort would give tighter occlusion, without improving flow.

In advanced uncomplicated anatomic emphysema the rigid restriction of expiratory flow, unresponsive to adrenalin and unremitting in the subsequent history of the illness, is precisely accountable to the inflexible properties of a checkvalve resulting from bronchiolar collapse. This mechanism fixes the ceiling on breathing capacity Abnormal intrinsic resistance in the airways caused by allergy or infection can, and often does, aggravate the handicap, but absence of this complication cannot alleviate it The same range and pattern of expiratory air flow results when Lung Tension is physiologically depleted. By contrast, adequate Lung Tension affords considerable protection against expiratory checkvalve closure when abnormal intrinsic resistance is present Flow is more ample during an acute, uncomplicated asthmatic seizure than it is in severe, but "dry" emphysema

The second outstanding protection is cartilage in the walls of downstream airways, which by location are subjected to greatest stress Within a certain range of compression, structural design enables them *to respond by partial rather than complete collapse* (Fig. 9 16) However, Valsalva pressures will tightly close the *normal trachea, and in poliomyelitis with respiratory paralysis we* have observed total collapse at less than 30 mm Hg pressure due *to atrophy of the tracheal cartilage.* Under pressure the membrane herniates into the lumen By contrast, mere encircling constriction, as with a strong cord, cannot occlude the trachea without causing wrinkling or overlap of cartilagenous plates, a point which emphasizes the dubious meaning of the term "bronchospasm" and directs attention to the bronchioles as the primary site of pressure regulation

Checkvalve narrowing of the major airways is necessary for effective cough It reduces flow but imparts a high linear velocity and high kinetic energy to the stream, which sweeps out secretions like projectiles from a gun Knowing rate of flow and cross section

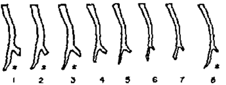

FIG. 9 16 Tracheobronchial dynamics, movie sequence of fluoroscopic image Eight consecutive frames showing tracheobronchial outline during cough from a sequence taken at sixty frames per second, courtesy of University of Rochester X-Ray Department and Dr Herman Rahn Subject was a woman, age 30, lipiodol bronchogram Inspiratory filling terminated at frame 1, and was followed by brief glottic closure At frame 3 the glottis was beginning to open At frame 4 the airways narrowed by $\frac{1}{3}$ (point of closure), and remained narrow Inspiration was just beginning at frame eight

There was a bolus of lipiodol in the bronchus intermedius The distance it extends toward the periphery approximately indicates the respiratory phase Because of its viscosity lipiodol cannot be swept out as easily as air and where a bolus fills the lumen the airway cannot collapse In such cases collapse occurs above and below the bolus, more so the former This accounts for the erroneous impression that bronchi exhibit peristalsis

Assuming a transverse internal tracheal diameter of 15 mm (x-ray silhouette in 10 adult women, mean 15 mm, range 12 to 21 mm, for 9 adult males, mean 18 3 range 16 to 20 mm), and a semicircular cross section, the area in frame 3 would be in the order of 100 sq mm, and in frame 4, 40 sq mm With these diameters peak flow of 7 l/sec at frame 3 would have a linear velocity of approximately 150 mi/hr Five liters per second flow at point of closure applied at frame 4, would give a linear velocity of 300 mi/hr See case reports at end of this section for flow rates during cough These approximations are of the same order of magnitude derived by Rahn from synchronous records of flow, esophageal pressure, and tracheal area

area of the trachea. Rahn calculated linear velocities in hundreds of miles per hour during the period of checkvalve narrowing (Fig 9 16) High volume rate of flow can be evoked by as simple a maneuver as sudden manual compression of the thorax but without sufficient pressure to narrow the airways it lacks the efficacy of cough Cough is not just a blast of air, but a complex mechanism nicely designed to clear the major airways of secretions Bronchiolar collapse in emphysema or excessive plugging upstream in atelectasis seriously undermines the efficacy of cough.

All checkvalves, intrathoracic airways included, are opened when flow is reversed Thus a bronchial tumor may not cause

detectable obstruction on inspiration yet occlude the airway completely on expiration. This is the mechanics of local obstructive emphysema in Case E F (Fig 9 9), and the basis for the localized palpable wheeze in tumor or stricture Similarly, intrinsic obstruction, in bronchial asthma, reduces expiratory more than inspiratory peak flow

Checkvalve phenomena do appear on inspiration but they arise in the upper respiratory tract. Diaphragmatic spasm causes the larynx to click shut in *hiccough*. Occlusive inspiratory collapse of the pharynx causes *snoring*. Checkvalve narrowing is physiologically solicited in *sniffing*, and through the same mechanical device high pressure, made possible by abrupt acceleration, causes checkvalve narrowing of the nares which directs a high velocity stream into the nasal passages to clear them of secretions.

A continuous record of air flow is known as a pneumotachygram In it one can demonstrate the effects of certain mechanical factors by employing breathing efforts designed to give them individual emphasis. We have found it helpful to include *quiet breathing* for comparison and for judging breathing reserve with respect to air flow

The pattern of flow for inspiration of maximum amplitude and speed (*maximum inspiration*) is studied for acceleration and peak flow, (V_P) which reflects the pressures applied by the subject, and indicates the more severe grades of intrinsic resistance Checkvalve phenomena, in the upper respiratory tract may impose variable changes in the range of peak flow (V_P), but fixed alterations are associated with pathologic states such as abductor laryngeal paralysis

Maximum expiration is the pneumotachygram counterpart of the vital capacity spirogram. Acceleration and peak flow are normally greater than those for inspiration; reversal usually indicates airway obstruction In health the duration of deceleration always exceeds that of acceleration, and obstructive conditions increase the disparity Checkvalve closure is indicated by sudden reduction of flow followed by the slower deceleration of *leakage flow* The angle in the tracing is designated Point Of Closure and under comparable conditions its must be present in every expira-

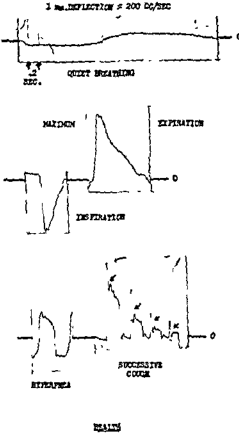

FIG. 9.17 Case G. S., a small, young woman, age 27, with no breathing handicap. *Quiet breathing.* Normal flow rates were present with aberrations due to heart beat. *Maximum inspiration.* Peak flow, $\dot{V}_P$ (downward deflection) 4.8 l./sec. *Maximum expiration.* Rate of acceleration was 100 l./sec., $\dot{V}_P$ = 6.2 l./sec., no POC but note that the pattern of deceleration cannot be altered by greater pressure (see cough). *Hyperpnea.* Suggestive POC was present on expiration. Laryngeal stridor probably affected inspiratory peak flow. *Successive cough.* $\dot{V}_{POC}$ = 4.4 l./sec., bronchial rebound was present. Note that the pattern of leakage flow was the same as that for deceleration in maximum expiration. *Interpretation.* The patient cooperated in the test. Lung Tension was normal. There was no abnormal airway resistance, respiratory neuromuscular function was good.

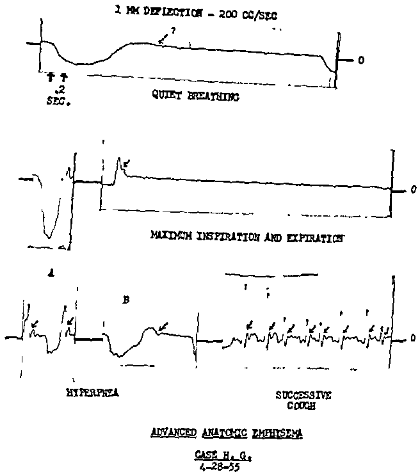

FIG 9 18 Case H G

METHOD Strain gauge Male, ht 6'3", age 43, severe anatomic emphysema with complicating bronchiectasis, working full time M M. V was 30 to 40 l /min depending on type of breathing effort The pattern of expiratory airflow was inflexible in more than 300 expirations analyzed over the course of four years

Quiet breathing Suspicion of expiratory POC was confirmed by more forceful efforts *Maximum inspiration* Inspiration $\dot{V}_P$ = 4 4 l /sec , but volume was low, acceleration was good *Maximum expiration*· $\dot{V}_P$ = 1 8 l /sec , $\dot{V}_{POC}$ = 1 l /sec POC occurred almost immediately Leakage flow quickly dropped to 0 4 l /sec or lower *Hyperpnea* (A) Sharp expiratory effort produced early POC. (B) Gentle effort augmented volume output of air The patient could improve M M V by 25 per cent through this maneuver *Successive cough* POC immediately followed brief extrusion of dead space air. Bronchial rebound caused small inspiratory flow during an expiratory effort showing that obstruction was present upstream to the large airways Note how the pattern of leakage flow resembled that of maximum expiration *Interpretation* Severe loss of Lung Tension is exhibited In spite of the history of bronchiectasis there was no appreciable generalized intrinsic airway resistance Inspiratory mechanics of the musculo-skeletal bellows was still good One would not anticipate response to bronchodilators nor to pneumoperitoneum (clinically confirmed).

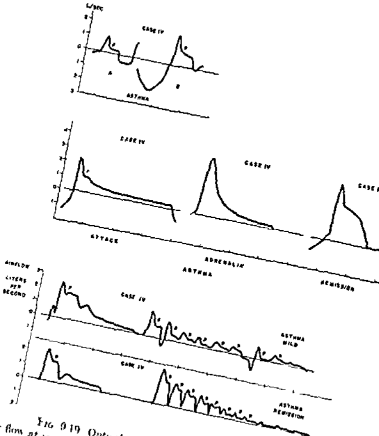

Fig. 9 19 Optical Case IV. An asthmatic adult male

Air flow at rest but during this an asthmatic seizure is shown, at A, (upper tracing). Distinct POC attests severity of the attack but there is far more flexibility than one finds in advanced emphysema. Under the stimulus of exercise, at B, air flow improved. The change in flow at POC is particularly significant. Maximum expiration (middle tracings) during attack showed a continuation of the leakage flow pattern with progressive slow deceleration. Adrenalin afforded the patient considerable relief but the asthmatic pattern of deceleration was not entirely abolished. It resembles that of bronchitis. Cough during a mild attack (lower tracings), showed improved flow at POC. One year later the patient declared his asthma to be entirely in remission and the pattern of flow for maximum expiration suggested it but the higher pressures of successive cough showed that remission was by no means complete. One would infer that the the principal handicap to breathing was intrinsic obstruction and that Lung Tension was good perhaps normal

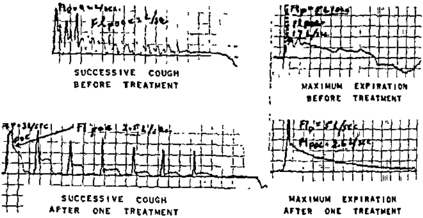

FIG. 9 20. Case E S.

Method Strain Gauge Male, age 64, was referred for treatment of emphysema Maximum expiration and successive cough was marked by erratic flow but at POC it was 1 7 and 2 0 l /sec respectively. Leakage flow progressively declined as the lungs deflated Treatment with a bronchodilator aerosol improved flow. Findings indicated that appreciable Lung Tension was still present, that some of the dyspnea could be ascribed to airway resistance After treatment with bronchodilators the patient was able to work in comfort

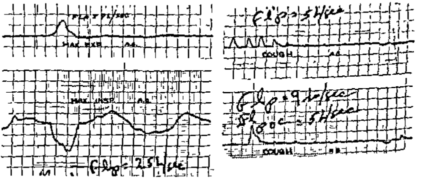

FIG 9 21 Case A C.

Method Strain Gauge Male, age 75, ambulant and working as an attorney, but with considerable dyspnea due to universal interstitial fibrosis Inspiratory

tion of threshold or greater force to differentiate it from erratic flow The volume exhaled before Point Of Closure, the flow at Point Of Closure (V_{POC}) and the pattern of leakage flow aid in appraising Lung Tension when comparison is made in other breathing maneuvers

That referred to as *hyperpnea* involves a panting type of breathing which emphasizes acceleration This produces marked and and sudden changes in pleural pressure Since tidal volume is small, Lung Tension is relatively constant

Successive cough beginning at position of maximum inspiration is essentially a maximum expiration interrupted by glottic closures, but the latter enables the subject to mount the highest at-

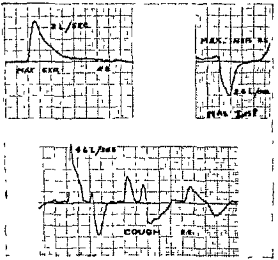

Fig 9 22 Case R S

Method Strain Gauge Male, age 64, one of three siblings to die of interstitial fibrosis in the seventh decade of life When tests were made the patient was bedridden and approaching fatal termination of the disease Weakness accounts for poor acceleration and overall reduction of peak flow But the relationships were nevertheless distinctive. The principal handicaps were small lung volume and limited inspiratory flow Cough (lower tracing) was initiated at something less than the position of maximum inspiration with the result that he ran out of air, so to speak, with one cough, and thus could not cough successively without interposing inspirations

tainable pressure In conditions where airways are unobstructed and Lung Tension is high, this may be the only way in which Point Of Closure can be detected. The general pattern duplicates that of maximum expiration, confirming the fact that the deceleration pattern is valid and cannot be altered by greater pressure, since it is defined by the checkvalve mechanism.

The case reports in Figures 9.17 to 9 23 illustrate effects of normal and abnormal breathing mechanics on the pattern of air flow *Some pneumotachygrams were made with a slow frequency* optical device which damps out brief extreme peaks of flow.

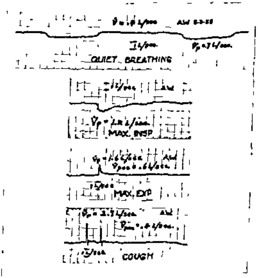

FIG 9 23 Case A W.

Method Strain Gauge Male, age 56, had severe anatomic emphysema with marked diaphragmatic inversion M M V. was 18 l *Quiet Breathing* Peak flow was in the order of 0 2 to 0 4 l /sec *Maximum inspiration* Peak flow was markedly reduced and every breath characterized by fair initial acceleration, a period of erratic flow, and protracted deceleration *Maximum Expiration* Peak flow ... flow was 0 2 to 0 05 l /sec, ... Peak flow was higher but ... to bronchial milking only.

Bronchial rebound was 0 8 l /sec *Interpretation* Lung Tension was virtually absent. (The lowest static pleural pressure recorded during a spontaneous pneumothorax was −5 cm water pressure) Marked thoraco-abdominal antagonism due to diaphragmatic inversion.

Others were made with a Statham P97 transducer and a Sanborn amplifier/recorder, which introduces artifact from turbulence, voice, vibration, etc Type of apparatus is not so important as the observers understanding of it It has been rewarding to find that the pneumotachygraphy gives meaning to many clinical manifestations of chest disease. The reader should view them as a means to this end

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This stimulating report deals with total capacity, Compliance, and spirometric analysis, and offers the thesis that ventilatory difficulty in emphysema is directly accountable to "loss of elasticity " The methods and interpretations have been challenged but much of the subsequent work on pulmonary function was stimulated by the need to test their validity

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This report deals with the change in alveolar shape during ventilation in health and correctly emphasizes the eradication of identifiable elements of normal architecture in anatomic emphysema

KOUNTZ W B AND ALEXANDER, H L Emphysema Medicine **13**: 251, 1934

This is a good comprehensive review

LAENNEC R T H *A Treatise on Diseases of the Chest* New York, Samuel S and William Wood, Translated from the third French edition 1838

This is a fundamental reference not only on the mechanics of respiration but on pathology and clinical aspects of chest disease Laennec's observations were so accurate and his deductions so penetrating that we find

ourselves quoting him verbatim, usually without recalling the source Unfortunately certain errors persist to this day as well. A student who wishes to trace the thought on mechanics of breathing in emphysema should begin by analyzing the paragraph by Laennec which follows (page 167)

"Pulmonary Emphysema supervenes almost always to an extensive and severe dry catarrh These facts lead us to a simple explanation of the mechanism of dilatation of the air cells It has already been shown that, in the dry catarrh, the smaller bronchial tubes are frequently completely obstructed either by pearly sputa or by swelling of their inner membranes Now since *the muscles of inspiration are numerous and powerful, while expiration, on the other hand, is produced merely by the elasticity of the parts and by the feeble contraction of the intercostal muscles,* it must frequently happen that the air, which during inspiration had overcome the resistance opposed to its entrance by the tumid state of the bronchial membrane and the sputa, is unable to force the same obstacles during expiration and remains therefore imprisoned in the cells by a mechanism somewhat *similar to the valve of an airgun* The succeeding inspirations, or at least such of them as are energetic, introduces a fresh supply of air into the same cells and thereby necessarily occasions their dilatation, and providing the obstruction is of some continuance, the dilated condition of the cells will be rendered permanent"

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in 1861

ROSS, B B, GRAMIAK, R, RAHN, H Physical Dynamics of the Cough Mechanism J Applied Physiol, 8: 264, 1955

I wish to acknowledge the kind interest of Doctor Herman Rahn, Department of Physiology, University of Rochester School of Medicine, who suggested taking moving pictures of the airways under the fluoroscope The studies were carried out in collaboration with Doctor B B Ross of the De

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STEAD, W W, FRY, D L, AND EBERT, R V The elastic properties of the lung in normal men and in patients with chronic pulmonary emphysema J Lab & Clin Med, 40: 674, 1952

These reports contribute important data on Compliance and resistance to air flow

Chapter 10

ADMINISTRATION OF BRONCHODILATOR AEROSOLS AND THE USE OF INTERMITTENT POSITIVE PRESSURE BREATHING (IPPB)

R DREW MILLER, M D, WARD S FOWLER, M D, AND H FREDERIC HELMHOLZ, JR, M D

The use of intermittent positive pressure breathing (IPPB) to administer O_2 and bronchodilator aerosols, as introduced in 1948 by Motley, Lang and Gordon, has created considerable clinical interest. However, agreement has not yet been reached on various problems that arise in the application of IPPB to the therapy of pulmonary emphysema. Some of the effects of IPPB, particularly in patients with pulmonary disease, are as yet incompletely understood. The eventual role of IPPB in the treatment of emphysema will be clarified as further clinical studies become available

Physiologic Considerations*

Intermittent positive pressure breathing (IPPB) customarily consists of the application to the upper airway of gases at pressures which exceed the ambient atmospheric pressure by periodically varying amounts This may be done in either of two ways Pressure-tight masks or mouthpieces may be connected to a mechanical valve which periodically delivers compressed gases from an external source, usually a gas storage cylinder, and this procedure is customarily known as IPPB. Another procedure which with certain qualifications is the physical equivalent is the use of a tank respirator In the latter case the pressure at the air-

* Various review articles pertaining to pressure breathing and aerosols have been written by Barach and associates, Whittenberger and D'Autrebande

way remains atmospheric, but the pressure around the body is periodically reduced below atmospheric In both cases a difference of pressure is created between the upper airway and the outside of the thorax

With establishment of a positive pressure difference, that is, airway pressure exceeding extrathoracic pressure, the lungs tend to expand However, the events that occur thereafter depend on the characteristics of the apparatus and also of the subject The major characteristics of the patient are the resistance to flow of gases in the airway and to motion of the pulmonary tissues, the pulmonary distensibility or compliance, and the characteristics of the thoracic wall The latter in turn depend both on the compliance of the nonmuscular tissues and on the amount and direction of muscular activity The major pertinent characteristic of a mechanical valve for delivering compressed gases is its own flow resistance, including opening pressure, which determines the rate of flow of gas that is delivered for a certain pressure difference between the line pressure and mask pressure When, during inspiration, pressure in the valve-mask system reaches a certain level, the mechanical valve closes * During expiration the flow of gases from the lungs is against the resistance of the airway and the expiratory valve of the apparatus, and may be produced by the elastic recoil of the lungs (and probably of the thorax at near-maximal lung volumes), expiratory muscular effort or both These points emphasize that the performance of a particular IPPB machine, or the mask-pressure curve obtained with its use, depends to a large extent on the respiratory characteristics of the person to whom it is attached The principal apparent feature of IPPB is that it can reduce or eliminate the work normally required of the respiratory muscles to achieve an inspiration, if used properly

Pulmonary Overdistention

Application of positive pressure breathing requires consideration of possible traumatic overdistention, with interstitial emphysema, pneumothorax and arterial gas embolism Rupture of the

* Functional characteristics of valves made by different manufacturers vary somewhat

lungs is not produced by high levels of alveolar pressure *per se*, but by excessive stretching. Alveolar pressures as high as 150 mm. of mercury are reached during a cough, but the lungs are not overdistended, for the intrapleural pressure increases almost as much because of expiratory muscular activity, which "splints" the thoracic wall It is apparent that the amount of pulmonary distention produced by application of a certain positive pressure to the airway depends on several factors. These are mainly the flow resistance in the airway, the distensibility of the lungs, the state of the thoracic wall, and how long the pressure is applied Flow resistance dissipates some of the applied pressure, and alveolar pressure during inspiratory flow will be less than mask pressure. The thoracic wall may, by voluntary or reflex muscular activity, either assist or oppose pulmonary inflation. The amount of distention resulting from the interaction of these factors will depend on the initial volume of the lungs, the rate of inspiratory flow and how long it is maintained. With the presence of regions of the lungs having different compliances and resistances, such as is probable in pulmonary emphysema or bronchoconstriction or both, the situation is more complex A relatively large pressure applied for a certain period may inflate a region with bronchoconstriction only moderately, but may dangerously distend a region of low resistance and high compliance The safe limits for a *maintained* pressure difference across the lungs (airway to pleural space) are not well established, either for normal or for diseased lungs, but are customarily regarded as 20 to 30 mm of mercury

Circulatory Effects

With normal inspiration, intrathoracic pressure becomes more negative relative to atmospheric pressure, and increases the venous-pressure gradient between intrathoracic and extrathoracic vessels, thus producing a transient increase of venous return and assisting the maintenance of cardiac output With inspiratory positive pressure, part of the increased pressure is absorbed by the lungs, but part appears as an elevation of intrathoracic and right atrial pressure, so that venous return is impeded. However, with a normal circulatory system, a compensatory rise of periph-

eral venous pressure occurs, with peripheral vasoconstriction, and venous return and cardiac output tend to be restored. When the circulatory system is impaired, as by a reduced blood volume or ineffective vasoconstriction, the compensatory increase of peripheral venous pressure is limited, and cardiac output is reduced The impeding effect of positive intrapulmonary pressures on the systemic circulation is roughly proportional to the magnitude of positive pressure and the fraction of the respiratory cycle during which it is present If mask pressure returns to near-atmospheric pressure during the expiratory half of the respiratory cycle, the embarrassment imposed on a normal circulatory system is probably not of great practical importance

The effects of variations of intrapulmonary pressure on the alveolar capillaries are not well understood, and depend on local or intrathoracic events as well as on the effects secondary to changes of the systemic circulation Although there are recurring suggestions that positive alveolar pressure compresses alveolar capillaries, the presence or magnitude of such an effect is uncertain and in dispute

Respiratory Effects

IPPB causes a variable increase of respiratory minute volume, usually by an increased tidal volume, both in normal persons and in patients with pulmonary disease This results in a decrease of the alveolar and arterial CO_2 tension, an increase of arterial pH and oxygen tension, and an initial period during which there is "blowing-off" of CO_2 However, after some minutes, even though hyperventilation continues, the alveolar concentration of CO_2 approaches a new and reduced level, which when multiplied by the increased rate of alveolar ventilation, yields a value for rate of CO_2 elimination which is equal to the rate of CO_2 production by the tissues, and thereafter "blowing-off" of CO_2 is not accomplished, although lower arterial CO_2 tensions are maintained It is of interest that the respiratory center, which normally maintains arterial pCO_2 within narrow limits, permits a marked reduction to occur during IPPB, even though it would appear still to have control over the depth and frequency of breathing

It is difficult to generalize as to the respiratory pattern which may occur after cessation of the period of hyperventilation produced by IPPB, and which determines the extent to which the previously reduced levels of CO_2 tension are maintained The ability to reduce arterial pCO_2 with a 10 to 20-minute period of IPPB is no guarantee that it will remain reduced, and the excess amounts of CO_2 that may be eliminated during a short period of hyperventilation are not impressively large relative to the hundreds of liters of CO_2 that are normally produced and eliminated in a day

Inspiratory positive pressure, if of sufficient amount and maintained during a sufficiently long inspiration, will inflate the lungs to a greater extent than is usual at the end of a normal inspiration With *pulmonary inflation, achieved either by IPPB or by natural* muscular activity, the bronchial tree also enlarges, with increased diameter of the various bronchi * However, even normal *pulmonary inflation is not uniform throughout the lungs Some* alveolar spaces receive more fresh air, relative to their preinspiratory volume than do others Unevenness of alveolar ventilation is greatly increased in pulmonary emphysema, *and large fractions* of the total lung volume receive very small amounts of fresh air with each breath during natural breathing at rest The physiologic mechanisms that are responsible are not well understood It is therefore difficult to predict whether or not the relatively underventilated regions of the emphysematous lung are ventilated differently when inspiration of a certain total volume is achieved with or without IPPB

In emphysema, there are also abnormally large variations in alveolar ventilation/perfusion ratio When the subject is breathing air, this leads to a lower arterial oxygen tension than would result from the same amount of alveolar ventilation if ventilation perfusion ratios were more uniform. The effect of IPPB on these abnormalities, as studied in coal miners by Motley and

* ...al after
cause

associates, appears to be variable In our opinion the changes following IPPB do not represent significant improvement in patients with abnormally large residual volume/total capacity ratios

It is appropriate at this point to mention aerosols, since IPPB has been widely used in an attempt to facilitate the delivery of aerosols of bronchodilator and other drugs to poorly ventilated regions of the lungs The delivery and deposition of aerosols within the lungs are subject to many factors, some of which are particle size, internal diameter of the respiratory passages, presence of secretions, and velocity and type of air flow through the passages Although with decreasing particle size the depth of penetration of an aerosol into the smaller air passages increases, the percentage of particles that are retained and not exhaled decreases. However, the retention can be increased by holding the breath for short periods at the end of inspiration, thereby facilitating deposition of the particles on the walls of the air spaces The intrapulmonary distribution of the type of aerosols that is generated by the most widely used nebulizers from solutions of bronchodilator drugs is largely limited by the flow of air into the various regions of the lungs, but need not coincide with it The uncertainties as to the effect of IPPB on improving the uniformity of alveolar ventilation in emphysema have been noted above, and apply similarly to its effect on the delivery of aerosols However, it seems reasonable and is consistent with clinical experience that deposition of aerosol can be augmented by any method that increases the at least potential delivery by adequate charging of the inspired gases with aerosol, by increasing the tidal volume, or by increasing the duration of the period of inhalation

IPPB has been said to provide breathing exercises and to improve muscle tone Both the definition of these effects and the manner in which they are achieved are not clear An abnormal pattern of use of the respiratory muscles is frequently observed in emphysema To what extent this is a result of altered reflexes for example from sensory receptors in the lungs or thoracic wall, and whether such reflexes are affected by IPPB remain to be demonstrated

dication to the use of sympathomimetic bronchodilators. Patients with severe angina pectoris or other types of circulatory insufficiency or cardiac irritability should not use large doses of these drugs

Administration of Bronchodilator by IPPB

IPPB apparatus is made by several manufacturers. All will provide IPPB, and each has certain relative advantages and disadvantages. Our principal experience has been with the Bennett apparatus (Fig 1), which has been quite satisfactory.

In practice IPPB has consisted of having the patient breathe oxygen, under positive inspiratory pressure, into which is introduced a continuous aerosol of bronchodilator or other drug During the expiratory phase some models of IPPB apparatus allow loss of the undeposited aerosol in the expired air and also loss of the aerosol generated into the apparatus by the nebulizer during expiration The latter, of course, is avoided with any method using inspiratory nebulization only Except for the loss of an un-

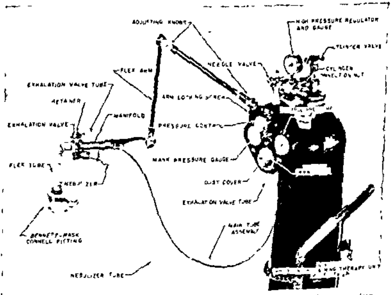

Fig 10 1 Intermittent positive pressure breathing (IPPB) apparatus

determined amount of rather expensive medication, the loss in the expired air is of little practical importance as long as the patient is benefited

The same basic principles of deep, slow breathing used in simple aerosol therapy also apply in IPPB It is important that the patient be informed of the purpose of the treatment, the manner of operation of the apparatus, and how to adjust and clean the nebulizer He should be instructed to breathe in a manner that, so far as possible, allows the positive pressure to take over the major work of inspiration and allows the valve to cycle with minimal effort Close supervision by trained personnel, preferably the physician, during the early phase of treatment is of utmost importance The use of only a few cm of water pressure on the first treatment and gradual increase to tolerated pressures in the range of 10 to 20 cm of water facilitate the patient's adjustment to the apparatus Tense patients who are not well indoctrinated may be frightened by the apparatus This obviously detracts from the benefits that can be derived

The dose of bronchodilator drug used with IPPB is similar to that in simple aerosol therapy The duration and frequency of treatment are also essentially the same

Complications

The untoward side effects enumerated under aerosol therapy also apply to IPPB Additional complications that have been reported during therapy with positive pressures have been pneumothorax and appearance of frank congestive failure with peripheral edema The first of these complications may be coincidental or may be related to the use of excessive levels of positive pressure without adequate preliminary use of gradually increasing positive pressure to determine the individual patient's tolerance By initiating treatment with lower pressures we have not personally observed acute complications Progressive right heart failure with peripheral edema presents a most difficult problem The various clinical, roentgenologic and electrocardiographic signs of cor pulmonale may be absent or equivocal until frank edema appears Although IPPB may not impair the function of a normal circula-

tory system, the periods of positive intrathoracic pressure ma impair venous return sufficiently in the presence of a failing righ ventricle that marked peripheral edema appears. IPPB cannot l considered the sole cause of this complication but may merel hasten the inevitable sequence of events We have noted th complication in several patients while they were on IPPB ha also in numerous patients on other forms of therapy.

Contraindications

The use of IPPB may actually be detrimental in the presence o pneumothorax or mediastinal emphysema Recent hemoptysis i a relative contraindication to IPPB. Careful attention must be given to possible circulatory changes when patients with CO retention are treated

Selection of Patients for Various Types of Aerosol Therapy

Some writers have advocated the use of IPPB for all patients with emphysema This is not a generally accepted belief, however.

Diffuse pulmonary emphysema, although a disease entity, frequently accompanies many other chronic pulmonary conditions such as chronic bronchitis, prolonged bronchial asthma, pneumoconioses (particularly silicosis), tuberculosis, bronchiectasis and some indeterminate forms of pulmonary fibrosis Consequently, patients in whom a diagnosis of pulmonary emphysema is made may present a wide variety of clinical problems This may account for some of the variety of effects reported with the use of IPPB in patients diagnosed as having pulmonary emphysema The patient's psychologic make-up, as well as the cardiovascular status, also influences the clinical response Ambulatory patients with moderate pulmonary disability due to emphysema but little or none of the afore-mentioned associated pulmonary conditions, in our experience derive similar subjective and objective benefit from daily use of aerosol bronchodilator with or without IPPB

Proponents of IPPB have reported subjective improvement in about 70 per cent of their patients (Smart and associates; Trimble and Kieran) Our studies confirm this incidence of improvement It is of interest, however, that in our control series of patients

using a similar program of bronchodilator aerosol, but without IPPB, 70 per cent also obtained subjective improvement. The nature of improvement in the two groups of patients was likewise similar. Moderate relief from dyspnea usually was noted on the first day of treatment, followed in several days by decreased cough and volume of sputum, decreased fatigue and varying degrees of improvement of appetite, sleep and sense of well-being.

Immediate but transient improvement in vital capacity and maximal breathing capacity of similar degree was usually noted after the initial aerosol treatment with or without IPPB (Table 1). Wu and associates reported similar findings in patients who do not have excessive secretions, but reported a more lasting immediate effect on the timed vital capacity and maximal breathing capacity with IPPB. Segal and associates stated that an aerosol with IPPB is superior to bronchodilator aerosol alone as measured by immediate improvement in the vital capacity.

Vital-capacity and maximal breathing-capacity measurements after a number of weeks of treatment showed only occasional improvement in our study when an aerosol with or without IPPB had not been administered since the previous day (Table 2). If

TABLE 1

Immediate effects of isoproterenol hydrochloride (Isuprel hydrochloride) aerosol on 31 patients†*

Test	Aerosol without IPPB‡: Before treatment	Aerosol without IPPB‡: After treatment, per cent of before	Aerosol with IPPB: Before treatment	Aerosol with IPPB: After treatment, per cent of before
Vital capacity	2.47 ± 0.10 L§ (46)	127 ± 3.7 (46)	2.56 ± 0.11 L (37)	121 ± 3.0 (37)
Maximal breathing capacity	30.8 ± 2.4 L/min (45)	130 ± 4.8 (45)	30.6 ± 2.4 L/min (37)	126 ± 3.9 (37)

* The Isuprel was furnished in part by Winthrop Laboratories, Inc.

† From Miller, R. D., Fowler, W. S. and Helmholz, H. F., Jr.

‡ IPPB = intermittent positive pressure breathing.

§ Values listed are the mean and its standard error. Number of observations in parentheses.

TABLE 2

Results of pulmonary function tests before and after 2 weeks of treatment with Isuprel aerosol, with or without IPPB

Test	Before Treatment	After Treatment*
Vital capacity	Reduced	Unchanged
Residual volume	Increased	Unchanged
Maximal breathing capacity	Reduced	Unchanged
N_2 washout index	Abnormal	Unchanged
Arterial O_2 saturation		
Rest	Few reduced	Some improved
Exercise	Many reduced	Some improved
Exercise tolerance	Reduced	Unchanged

* No treatment for at least 12 hours before this test

the tests were repeated at that time after another single treatment, *the immediate response was usually similar to that after the initial single treatment* Segal and associates have also reported results of this type Despite the lack of improvement in objective measurement, some of the subjective improvement described above usually persisted

The ideal goal of treatment would be both subjective and objective improvement. However, maintenance of objective findings at a constant state over a period of months and years should be encouraging to both the patient and the physician, for the natural history of diffuse pulmonary emphysema is one of relentless progression We have noted this maintenance of objective findings at a constant or sometimes improved level in patients treated for long periods with bronchodilator aerosols with or without IPPB

Of our patients who obtained subjective benefit from bronchodilator aerosols with or without IPPB, about one-third had a personal preference for the IPPB, stating that they "opened up" more at the time of treatment, another third preferred the effects of the aerosol without IPPB, and the remaining third had no preference

In ambulatory patients who have excessive bronchial secretions IPPB may in some instances offer significant additional benefit The only instances in which we have noted significant objective

improvement with IPPB which suggests possible superiority to aerosol alone have been in younger patients, particularly those with more than ¼ cupful of mucoid or mucopurulent sputum daily. This type of case represents a minority of the patients whom we see clinically with pulmonary emphysema In practice, it has been our policy to have younger patients with emphysema, and who have excessive sputum, try a period of supervised treatment with aerosol bronchodilator alone and subsequently also with IPPB If the latter method results in objective or subjective improvement beyond that of aerosol alone, arrangements are made for longer use of IPPB Some type of bronchodilator aerosol therapy with or without IPPB should be continued in patients with subjective improvement for many months to achieve a maximal effect on the reversible aspects of the chronic disease process

Chronic CO_2 Retention with Respiratory Acidosis

Much has been written about the problem of carbon dioxide retention in hypoxemic patients with emphysema The respiratory center may become relatively insensitive to elevated CO_2 tension, and the hypoxemic stimulus to breathing gains in relative importance Barach, Comroe and associates, and Lovejoy and associates have described the biochemical and clinical consequences of the removal of the hypoxemic stimulus by administration of high concentrations of oxygen Hypoventilation develops with marked increase of CO_2 tension and decrease of pH of the arterial blood, *resulting in central nervous system depression and even death* Barach has advocated a simple and usually effective method for combating these acute consequences of oxygen therapy Oxygen is administered by nasal catheter initially at a flow of 1 liter per minute This is gradually increased to levels which relieve hypoxemia but do not result in excessive depression of ventilation If more rapid relief of hypoxemia is desired, mechanical aid to respiration is of value in maintaining ventilation adequate to prevent further CO_2 retention This can be achieved with either a body-type or face-mask respirator

Lovejoy and associates reported disappointing results using one

TABLE 3
*Pulmonary emphysema, changes in arterial blood**

	Arterial pH	O_2 Capacity	O_2 Content	CO_2	P_{aCO_2}
		vol %	vol % (% sat)	vol %	mm Hg
Breathing air	7 38	21 4	18 1 (84%)	61 2	54
O_2 mask for 10 min	7 34	20 5	21 7 (100%)	63 0	60
O_2 IPPB for 8 min	7 40	20 7	21 9 (100%)	59 0	51

* During breathing of oxygen by mask and during intermittent positive pressure breathing

type of mask respirator in this syndrome, and expressed preference for the use of a body-type respirator Segal and associates and Cohn and associates described the effective use of a mask type of respirator if its use is under close surveillance of trained personnel. As have others, we have found IPPB to be effective in preventing an acute retention of CO_2 following administration of high concentrations of O_2 Table 3 shows the increase in arterial CO_2 tension in a patient with severe emphysema, while breathing oxygen by mask In contrast the CO_2 tension is decreased while using IPPB-oxygen without a bronchodilator. The maintained prevention or relief of CO_2 retention, however, requires numerous periods of assisted respiration Of equal or greater importance is vigorous use of bronchodilators and often antibiotics, with additional use of digitalis and diuretics if congestive failure is present Diuretics should be used with consideration of the effects on renal compensation for electrolyte disturbances in such cases

PROGNOSIS

Despite these numerous measures in managing CO_2 retention and respiratory acidosis the outlook is poor, chiefly because of the irreversible anatomic changes in the lung in this advanced stage of emphysema If the CO_2 retention is precipitated by an acute complication such as bronchopulmonary infection, then a prolonged remission can often be achieved by utilizing some features of the above therapeutic program

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Chapter 11

PHYSIOLOGIC CONSIDERATIONS IN MANAGEMENT RELATIVE TO THE DEVELOPMENT OF ACIDOSIS AND TO THE WORK OF BREATHING

JAMES K ALEXANDER, M D

The Development of Acidosis

The appearance of CO_2 retention in the arterial blood is a relatively late manifestation in the natural history of chronic pulmonary emphysema, usually indicating advanced disease. Although certain aspects remain conjectural, at present the sequence of physiologic events leading to respiratory acidosis in emphysema can be at least partially defined. In this section the nature of these events will be outlined, together with certain of their therapeutic implications.

Broadly speaking, the partial pressure or tension of CO_2 in the alveoli of the lung is dependent upon the rate at which CO_2 diffuses into the alveoli from the pulmonary capillaries, and the rate at which the alveoli are ventilated with fresh air. Thus the CO_2 tension of the arterial blood, in equilibrium with the alveolar CO_2 tension, varies directly with the CO_2 production of the body, and inversely with the alveolar ventilation. In advanced emphysema CO_2 production may be slightly increased because of the additional energy expenditure necessary to ventilate the lung. However, the arterial CO_2 retention at rest observed in the later stages of the disease is chiefly the result of alveolar hypoventilation. This reduction in effective alveolar ventilation occurs despite the presence of blood chemical stimuli normally bringing about

an increase in ventilation, namely anoxemia, acidosis, and hypercapnia. Yet these same patients are capable of significant increases in ventilation either on a voluntary basis or in response to exercise. These latter circumstances suggest that hypoventilation and CO_2 retention come about in these patients as a result of a disorder in the chemical regulation of respiration.

Experimental observations designed to characterize such a disorder in the control of respiration associated with emphysema cover a span of nearly half a century. As early as 1912, Reinhardt found that certain emphysematous subjects had a diminished ventilatory response to CO_2 inhalation as compared with the normal. This observation has been repeatedly confirmed. More recent studies have made it clear that the diminished respiratory response to CO_2 inhalation occurs in precisely those individuals previously suspected of having disordered ventilatory regulation, namely those with chronic alveolar hypoventilation and CO_2 retention.

In order to determine the mechanism by which the diminished response to CO_2 inhalation is brought about in such patients, it has been necessary to explore several possibilities. Increased buffering capacity of the blood, for example, associated with an elevated plasma bicarbonate level or polycythemia might result in a smaller increment in free hydrogen ion concentration in the blood on addition of a given amount of CO_2 and therefore a lesser ventilatory response. However, this is not the case, since with CO_2 inhalation blood hydrogen ion concentration in these patients rises more than in normal subjects and the ventilatory response is still less. Another consideration of possible importance in accounting for the diminished response might be the presence of a ventilatory defect of such severity that the chest bellows could not respond adequately to increasing nervous stimuli. This possibility has been eliminated by the finding that emphysematous patients with comparable ventilatory defects, but without CO_2 retention, have a normal response to CO_2 inhalation. Finally, certain other phenomena accompanying severe emphysema require evaluation as possible conditioning factors. These are associated congestive heart failure, chronic anoxemia, chronic acidosis,

and chronic hypercapnia itself Of these latter possibilities, it has been found that chronic hypercapnia *per se* is the one of crucial importance Heart failure is of no significance in this regard since patients with CO_2 retention have a diminished response whether failure is present or not, and patients with heart failure of other etiology have a normal response Similarly, patients without hypercapnia suffering from chronic anoxemia associated with cyanotic congenital heart disease, or chronic acidosis secondary to renal failure, show no diminution in the ventilatory response to CO_2 inhalation On the other hand, in the absence of lung disease, patients with chronic hypercapnia secondary to metabolic alkalosis are found to have a significant reduction in ventilatory response to carbon dioxide inhalation. These observations are summarized in Figure 1, which shows the sensitivity of the neural respiratory regulatory mechanism to the carbon dioxide stimulus in the various conditions mentioned above In Figure 1 sensitivity is defined by the slope of the stimulus response curves Stimulus is expressed as arterial carbon dioxide tension, and ventilatory

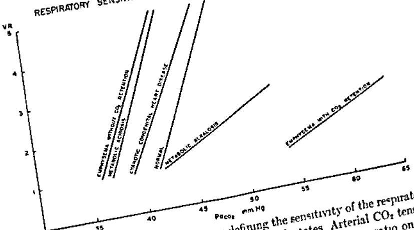

FIG 11 1 Stimulus response curves defining the sensitivity of the respirator neural regulatory mechanism in varying chemical states Arterial CO_2 tensi in mm Hg on the abscissa is plotted against alveolar ventilation ratio on t ordinate See text for discussion

response as the alveolar ventilation ratio This latter refers to the ratio between the observed effective alveolar ventilation and the alveolar ventilation at rest

It seems established that the presence of chronic hypercapnea *per se* results in a diminished sensitivity of the respiratory regulatory mechanism to the normal CO_2 stimulus These observations are consistent with the hypothesis of CO_2 adaptation advanced by Gray

It would seem reasonable to anticipate that increasing carbon dioxide retention might be accompanied by further loss in sensitivity of the regulatory mechanism Actually, sensitivity does tend to diminish with increasing arterial CO_2 tension at rest as shown in Figure 2 and Figure 3 Since CO_2 inhalation is associated with an increased stimulus to respiration in terms of arterial CO_2 tension and hydrogen ion concentration, sensitivity relative to these stimuli is plotted separately

In the light of the above considerations and certain other information, it is possible to formulate a tentative hypothesis re-

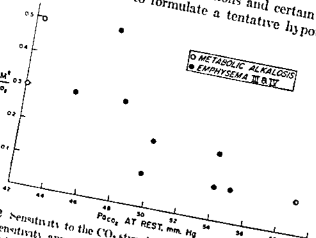

FIG 11 2 Sensitivity to the CO_2 stimulus as a function of the degree of CO_2 retention Sensitivity appears on the ordinate in terms of increase in effective alveolar ventilation (liters BTPS per square meter body surface area) associated with 1 mm Hg rise in arterial CO_2 tension On the abscissa is plotted arterial CO_2 tension at rest (From Alexander, West, Wood, and Richards)

garding the sequence of physiologic events leading to the development of CO_2 retention in emphysematous patients This hypothesis is outlined in Figure 4 At some point in the course of the disease the ventilatory capacity becomes insufficient to eliminate the additional CO_2 produced by the tissues during exertion, and transient rises in arterial CO_2 tension occur. Eventually these repeated bouts of hypercapnia result in a diminished sensitivity to the CO_2 stimulus, thus permitting an elevated arterial CO_2 tension at rest, although the ventilatory capacity may be such that a normal arterial CO_2 tension at an increased resting ventilation is possible An elevated arterial CO_2 tension at rest favors increased retention of bicarbonate by the kidney (Brazeau and Gilman, Dorman and associates) and thus a vicious cycle of increasing CO_2 retention, diminishing respiratory sensitivity, and hypoventilation is initiated

At least two therapeutic objectives emerge from these physio-

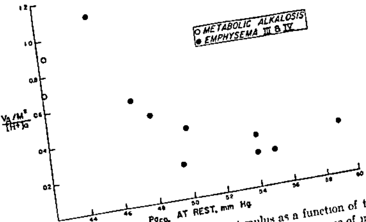

FIG 11 3 Sensitivity to the hydrogen ion stimulus as a function of the de gree of CO_2 retention Sensitivity appears on the ordinate in terms of increas in effective alveolar ventilation (liters BTPS per square meter body surface area associated with unit rise in arterial hydrogen ion concentration (billionths moles per liter) On the abscissa is plotted arterial CO_2 tension at rest (Fro Alexander, West, Wood, and Richards)

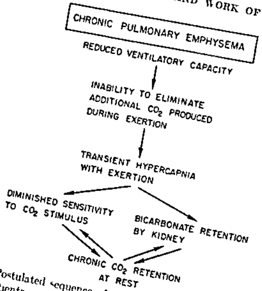

FIG 11 4 Postulated sequence of events leading to chronic carbon dioxide retention in patients with obstructive pulmonary emphysema

logic considerations relative to the development of respiratory acidosis They are (1) prevention of the appearance and progression of CO_2 retention, and (2) restoration of a normal sensitivity to the CO_2 stimulus, where modification may have already occurred

Since detailed discussion of therapeutic procedures aimed at accomplishing these objectives will be found elsewhere in this book, only a few general remarks will be made in this connection here In regard to the first objective mentioned above, notable circumstances giving rise to transient CO_2 retention in susceptible individuals or to transient increases in CO_2 retention are acute pulmonary infection and vigorous physical exertion If hypercapnea and anoxemia are already present, prolonged oxygen inhalation will result in further alveolar hypoventilation, CO_2 retention, acidosis, and diminution in "respiratory center" sensitivity The matter of restoration of sensitivity to chemical stimuli in an already depressed "respiratory center" requires further study

It is not clear at this time whether a normal or improved sensitivity to the CO_2-hydrogen ion stimulus can be obtained in patients with chronic hypercapnia and established depression relative to this stimulus Nevertheless, mechanical measures directed toward increasing the effective alveolar ventilation in this chronic state of respiratory depression will bring about transient improvement in anoxemia, hypercapnia, and acidosis In addition, depletion of plasma and tissue bicarbonate with diminished hypercapnia may be effected by drug therapy In both instances, it might be hoped that improvement in the degree of hypercapnia would be accompanied by a tendency toward restoration of normal "respiratory center" sensitivity, permitting a sustained alveolar ventilation of normal volume

The Work of Breathing

From the symptomatic point of view probably the most distressing and most frequently observed problem in pulmonary emphysema is that of dyspnea Dyspnea, the subjective sensation of difficulty in breathing, characteristically appears at first only during physical exertion, later becoming more severe until it is present at rest as well Since dyspnea in its strictest sense refers to a subjective sensation, it presumably depends upon a neural mechanism involving receptor, transmitting, and integrating units At present there is insufficient information to permit definition of dyspnea in these terms However, in a larger sense, the dyspneic state associated with chronic lung disease is subject to analysis in the light of existing knowledge Such a concept of dyspnea, based upon a combined clinical and physiologic approach, has been recently advanced by Richards. According to this schema, the appearance of dyspnea is dependent upon the interrelationships between ventilatory drive and breathing mechanics Ventilatory drive, largely a physicochemical or neurogenic function, determines the actual level of ventilation or breathing requirement for any given condition of rest or stress Factors of importance relative to breathing mechanics are (1) the individual's ventilatory capacity, usually quantitated in terms of the

maximum breathing capacity, and (2) the energy expenditure by the muscles of respiration necessary to achieve a given pulmonary ventilation, or the work of breathing Dyspnea is favored by any circumstance making for an imbalance between the breathing requirement and respiratory mechanical performance Such an imbalance may be effected by hyperventilation on the one hand, and by reduced ventilatory capacity or increased respiratory work on the other Chronic pulmonary emphysema may give rise to all three of these situations In this section discussion will be limited to a consideration of manner in which disordered ventilatory function in emphysema brings about increased respiratory work, the magnitude of the increment, and therapeutic reduction in the work of breathing

Estimation of respiratory work may be approached in various ways The amount of work done may be roughly approximated if information is available regarding the cross sectional area of the respiratory muscles, the degree of shortening which occurs during contraction, and the magnitude of the forces involved A second approach is measurement of the increased oxygen utilization brought about by voluntary hyperventilation In this way the total energy required for breathing may be estimated as a function of oxygen consumption Finally, the work of breathing may be expressed mechanically as the sum total of the energy developed to distort the lung and chest wall, as well as to provide motion to these structures and the air within the lung Analyzed in the conventional manner, the mechanical resistances to be overcome by the respiratory muscles in producing lung ventilation fall into four categories (1) The restoring force exerted by the lung and thorax when the structures are inflated This has been termed elastic resistance or compliance (2) The force required to overcome frictional resistance in the living tissue, or "tissue viscance" (3) The force required to overcome resistance to air flow within the respiratory air passages (4) The force required to overcome inertia of the lung and thorax and of air and blood within the lung This latter force is presumably very small

That chronic obstructive emphysema may lead to a considerable increase in the work of breathing is well established Cournand

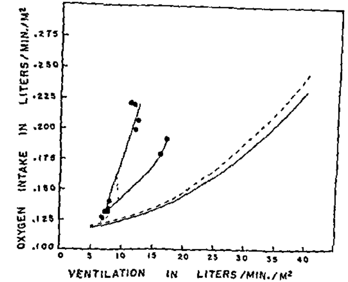

FIG 11.5. Oxygen cost of hyperpnea in chronic pulmonary emphysema. The open circles and dark circles represent observations at respiratory frequencies of 20 and 30 respectively Measurements were obtained before and after partial relief of bronchial obstruction Normal values for comparison at respiratory frequencies of 20 and 30 are indicated by the broken line and solid line curves respectively (From Cournand, Richards, Bader, Bader, and Fishman)

and co-workers found the oxygen cost of breathing in a patient with emphysema higher than normal by making direct measurements of oxygen consumption at varying rates of voluntary hyperventilation

These findings are illustrated in Figure 5, showing the oxygen cost of hyperpnea in this patient as compared with the normal For an increase in ventilation of 5 l./min, the patient required an increment in oxygen uptake comparable to that required for a ventilation increase of more than 50 l /min by the normal subject From the therapeutic standpoint, the results of measurements obtained on two different occasions in this emphysematous patient are noteworthy Following partial relief of bronchial obstruction, the oxygen cost per liter of ventilation over the resting level fell to approximately 25 per cent of its previous value

Similarly, estimation of the mechanical work necessary to venti-

late the lung in emphysematous subjects by McIlroy and Christie indicates that the work rate per minute necessary to achieve a given ventilation may be much greater than normal. A patient with emphysema may have to do as much respiratory work while breathing at 15 l./min. as a normal subject breathing at 30 or 40 l./min.

Further analysis of the augmented respiratory work in emphysema with reference to the resistive forces previously mentioned has been at least partially successful. These observations deal almost entirely with the work of ventilating the lung alone, as estimation of the work required to move the thorax and abdominal contents in these patients is difficult. As a convenient approach to the problem, the total energy expenditure required to ventilate the lung may be subdivided into two chief components. That portion of the total required to overcome resistance to tissue deformation and air flow in the lung may be considered the resistive component. That portion required to overcome the elastic resistance or restoring force of the lung may be considered the elastic component. In normal individuals the elastic component of respiratory work accounts for approximately two-thirds of the total at rest, and within limits is independent of respiratory rate. On the other hand, the resistive component varies directly with respiratory rate. This relationship between the two components does not hold in emphysema, however. As pointed out by Mead and associates, with higher respiratory frequencies the flow resistive properties of the lung exert a greater effect upon the distribution of flow to its various parts, so that a progressively smaller lung volume is effectively ventilated. This results in an apparent increase in the elastic component with higher respiratory rates and makes differentiation of total work into two components a rather arbitrary thing. Measurement of elastic work required to inflate the emphysematous lung under static conditions or during quiet breathing over the range of the tidal volume yields a normal or slightly increased value. On the other hand, resistive work in emphysema is strikingly *increased over the normal at any given frequency*. In Figure 6 and Figure 7 are shown contrasting pulmonary pressure volume loops in the normal and emphysematous

states, which permit estimation of the respiratory work for a given breath, and differentiation of its two major components If, during a single breath, simultaneous measurements are made of the change in the volume of the lung and the change in intrathoracic pressure necessary to accomplish this, a dynamic pulmonary pressure volume loop may be constructed. Using intraesophageal pressure as equivalent to intrathoracic pressure, such a loop is plotted in Figure 6 for a normal subject breathing at a respiratory frequency of 20/min The pressure observed at the peak of inspiration when no air flow is occuring represents the static pressure necessary to overcome the elastic forces in the lung

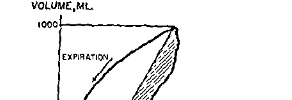

FIG 11.6 Dynamic pressure volume loop for a single breath at a respiratory frequency of 20 in a *normal individual* On the ordinate is plotted lung volume change in ml Transpulmonary pressure increment on the abscissa indicates *the differential pressure* in cm water between mouth and intraesophageal *pressure* taking the latter as equivalent to *intrathoracic pressure* Zero on the abscissa *refers* to intraesophageal pressure at the end-expiratory position, and *positivity or negativity* to change relative to this value See text for discussion *

* *This type of representation* takes no account of the work necessary to expand the lung to the *end-expiratory* position, and therefore the calculated elastic work is inaccurate It affords, however, a convenient *means of contrasting the* normal and emphysematous states

at that volume. Such a relationship, obtained at varying lung volumes, determines the static pressure volume curve, or compliance of the lung, and is designated by the line within the loop. At a given instant in the respiratory cycle, the difference between the observed pressure and the compliance curve will indicate that pressure increment required to overcome the frictional resistances associated with movement of air and tissue. It will be recognized that the areas described by a diagram of this kind are directly related to mechanical work performed, and may be expressed in units of work. Thus the elastic work for the breath shown in Figure 6 is defined by a triangular area bounded by the compliance curve, a line drawn from the peak of the compliance curve perpendicular to the ordinate, and the ordinate itself. This area also represents potential energy stored during inspiration which is presumably available to aid in overcoming expiratory resistances. The inspiratory frictional or resistive work is shown in the shaded area bounded by the inspiratory portion of the loop and the compliance curve. The expiratory resistive work, described in the area

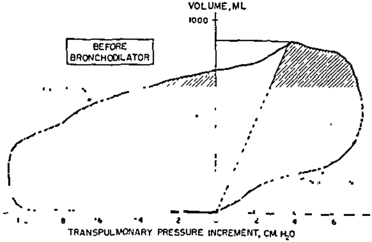

FIG. 11 7. Dynamic pressure volume loop for a single breath at a respiratory frequency of 16 in a patient with obstructive emphysema. The physiologic variables are plotted as indicated in Figure 11 6. See text for discussion.

bounded by the expiratory portion of the loop and the compliance curve, is unshaded. In this case, the potential energy stored in accomplishing the inspiratory elastic work is more than adequate to overcome the expiratory resistance and no additional work is done during expiration. Therefore the total work for this breath is represented in the area bounded by the inspiratory portion of the loop, the line from the peak of the loop perpendicular to the ordinate, and the ordinate itself The lung compliance in Figure 6, defined by the slope of the line within the loop, is 0 185 l/cm water pressure The total calculated work for the breath is 1 4 kilogram meters × 10^{-2}, of which approximately 70 per cent is elastic and 30 per cent resistive.

In Fig 7 is shown the pressure volume loop for a breath of approximately the same volume at a comparable respiratory frequency in a patient with obstructive emphysema. It can be seen that the lung compliance, and therefore the amount of elastic work, are nearly the same as the normal. However, an enormous increase in the total work has occurred by virtue of increased resistive work The potential energy stored during inspiration is no longer sufficient to overcome expiratory resistance, which has now become the predominant factor in conditioning the overall work requirement There is a complete reversal of the normal relationship, so that the resistive work constitutes 86 per cent of the total, and the elastic work only 14 per cent The total calculated work for this breath is 11 5 kg m. × 10^{-2} or over eight times that done by the normal subject

In Figure 8 is shown the pressure volume loop for a breath of comparable volume at identical frequency measured in this same emphysematous subject following bronchodilator* therapy Although the total work is still very considerable, and the relationship between elastic and resistive work is essentially unchanged, there is nevertheless a significant reduction in total work This comes about largely as a result of decreased resistive work, though the apparent compliance is somewhat greater also Calculated

* "Vaponefrin," a 2 25 per cent solution of racemic epinephrine as hydrochloride

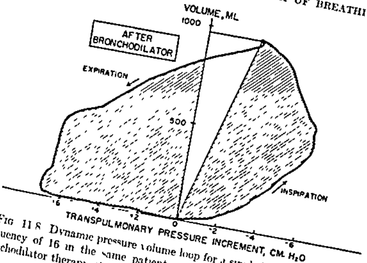

FIG 11 8 Dynamic pressure volume loop for a single breath at a respiratory frequency of 16 in the same patient with obstructive emphysema following bronchodilator therapy See text for discussion

total work for this breath is 8 8 kg m $\times 10^{-2}$ or about 75 per cent of that required before bronchodilator therapy

Summarizing, the disturbances in ventilatory function associated with chronic pulmonary emphysema lead to greater respiratory work Appearance of dyspnea, the chief symptom of disordered ventilatory function, is partially related to the degree of increase in the work of breathing Relief of dyspnea, an important therapeutic objective, will be conditioned to a certain extent by the success with which reduction in respiratory work can be accomplished As a convenient example of the means by which appreciable reduction in respiratory work may be effected, bronchodilator therapy is cited

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Chapter 12

ROLE OF INFECTION IN CHRONIC HYPERTROPHIC PULMONARY EMPHYSEMA

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Repeated pulmonary infections have long been recognized as perhaps the most important deleterious influence leading to deterioration of pulmonary function in chronic pulmonary emphysema Antimicrobial therapy has been enormously helpful in these cases, and in the decade and more of its use certain procedures and principles have emerged to guide treatment Despite these favorable results the relative role of the various infectious agents in the complicating respiratory infections, and the most suitable methods of employing antimicrobial therapy, remain uncertain In this chapter is presented a review of the problem of infection in pulmonary emphysema with special emphasis on its diagnosis and treatment

Respiratory Diseases Associated with Pulmonary Emphysema

Several kinds of pulmonary disease may precede, accompany or complicate the course of chronic hypertrophic pulmonary emphysema In Table 1 are shown data in which the frequency of occurrence of these diseases in clinical and autopsy cases of emphysema is described (Whitfield, Scott and Garvin, Spain and Handler) Of particular interest in this Table is the finding that 70 to 80 per cent of cases of emphysema were associated with some kind of nontuberculous pulmonary infection, and in the largest proportion of cases chronic bronchitis was the type of disease described The

TABLE 12 1

Frequency of associated pulmonary diseases in cases of chronic hypertrophic pulmonary emphysema diagnosed clinically and at autopsy

Diagnostic Classification	Clinical Study: Whitfield, 1952		Autopsy Study*: Scott and Garvin, 1933		Autopsy Study*: Spain and Handler, 1946	
	No	Per cent	No	Per cent	No	Per cent
Emphysema, usually with bronchitis, no other recognized pulmonary disease, including four cases rapidly fatal without apparent infection	54	52.4	25	54.3	40	70.1
Emphysema, onset following pneumonia	10	9.7	No observation		No observation	
Emphysema and bronchiectasis	7	6.9	7	15.2	6	10.5
		69.0		69.3		80.6
Emphysema and tuberculosis (some with silicosis)	Intentionally excluded from consideration		7	15.2	5	8.7
Emphysema following bronchial asthma	19	18.4	No observation		6	10.5
Emphysema and silicosis	3	2.9	7	15.2	No observation	
Emphysema in patients "gassed" during war and one case of exposure to sulfur dioxide fumes	10	9.7	No observation		No observation	

* These cases constituted 103 of 108 cases of cor pulmonale studied at post mortem

data in the table are surprisingly uniform on this point, considering the wide geographic and time differences in the studies, in addition to the fact that in Whitfield's report diagnoses were based on clinical studies, and in the others the lesions were identified at autopsy. As an incidental finding, it was shown that among cases of chronic cor pulmonale detected at autopsy, the majority occurred in patients with chronic pulmonary emphysema, suggesting that the major cause for chronic cor pulmonale may be pulmonary emphysema

There was a consistent low rate of occurrence of bronchiectasis in patients with chronic pulmonary emphysema, its incidence ranging only from 6.9 to 15 per cent in the three series. This is logical since bronchiectasis tends to be a localized disease, and in even severe cases large areas of lung may be entirely uninvolved. Localized emphysema may be found in lung segments distal to areas of bronchiectasis but this disease is distinct from the generalized type of emphysema presently under discussion.

In these studies there was a frequent association of chronic bronchitis with emphysema. This relationship has led many observers to attach an etiologic role to chronic bronchitis in emphysema. In support of this view is the fact that in infants and children an acute bronchiolitis, often caused by encapsulated strains of *Hemophilus influenzae*, occurs, in which acute emphysema develops with a picture of pulmonary insufficiency very similar to that in chronic pulmonary emphysema (Wood and associates, Nelson and Smith). In these cases improvement from the infection coincides with relief from the acute emphysema. Moreover, Amberson and Spain have described clinical and post mortem findings in a case of chronic bullous emphysema in an adult which they feel arose from recurrent episodes of bronchiolitis. It was their concept that a chronic, organizing, constrictive bronchiolitis and peribronchiolitis occurred, and stiffened and narrowed the lumens of the bronchioles. They postulated that these changes led to the distention of alveoli and the other manifestations of chronic progressive pulmonary bullous emphysema in that case and others of the same type.

It is most logical to believe that in a definite proportion of cases of chronic pulmonary emphysema, infectious bronchiolitis has led to chronic constriction of bronchioles with the later development of emphysema. Whether such an occurrence may depend upon some inherent host susceptibility is not known, but it is reasonable to suppose that age, sex, general health, inheritance, occupation, or other factors might lead to a greater proneness of one person over another to emphysema following episodes of bronchiolitis.

Bronchitis in patients with emphysema is considered to be predominantly of infectious origin, but physical or chemical irri-

tants, and allergic reactions may initiate attacks of the disease Recently, Lowell and his associates have suggested that smoking may be an important predisposing cause of pulmonary emphysema Bronchitis may also be a manifestation of many other kinds of pulmonary disease. It frequently is present in patients with pulmonary carcinoma, heart failure, and tuberculous or mycotic infection It is important not to overlook the possible presence of these diseases in patients with bronchitis

Pathology of Bronchitic Lesions in Emphysema

The lesions of bronchitis at autopsy show considerable variation in their severity and location in the respiratory tract It is also believed that during the course of progressive emphysema consecutive episodes of bronchitis may involve widely different areas of the bronchial wall

Kountz and Alexander have described the pathologic lesions of bronchitis in cases of very advanced disease associated with bronchitis seen at autopsy In the smaller bronchi they found lesions resembling bronchiolitis obliterans with obstruction of lumens by chronic inflammatory tissue In the larger bronchi there appeared to be concentric ingrowth of inflammatory elements toward the lumens, and in others it was eccentrically located All the bronchial structures showed atrophic changes Muscle was thinned and patchy and did not completely encircle bronchi Glands were less numerous than normal The epithelium was low cuboidal and atrophic instead of columnar ciliated. The subepithelial layer on occasion was increased in thickness and infiltrated with lymphocytes The bronchi were dilated in areas and the whole picture could be described as one of a chronic inflammatory reaction with an outgrowth of granulation tissue.

In other cases of bronchitis and of bronchial asthma with emphysema, muscle hypertrophy has been described Few changes are found consistently throughout a single lung and especially in smaller bronchi muscle hypertrophy may predominate over atrophic changes

Pneumonia was not listed as occurring with great frequency

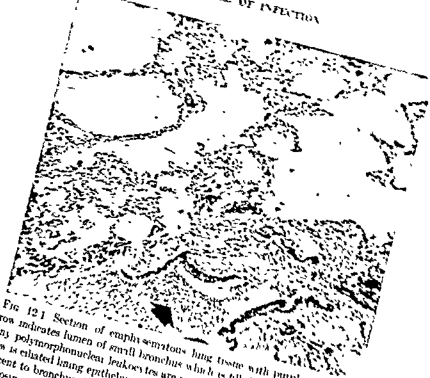

Fig 12 1 Section of emphysematous lung tissue with purulent bronchitis Arrow indicates lumen of small bronchus which is filled with purulent exudate Many polymorphonuclear leukocytes are present here Dark, irregular line near arrow is ciliated lining epithelium of bronchus Dilated and disrupted alveoli are adjacent to bronchus but show very little inflammatory reaction Hematoxylin and eosin, 42 × (Courtesy Dr David Beaver and Dr John Shapiro, Department of Pathology Vanderbilt University School of Medicine)

in either clinical or autopsy series of cases of emphysema Pneumonia undoubtedly does occur less frequently than recurrent episodes of bronchitis, but among cases of emphysema encountered in hospital practice pneumonia is not uncommon The only evidence from autopsies which may indicate previous episodes of neumonia is a high frequency of pleural adhesions

Bronchitis in emphysema is not usually severe enough in itself cause death, but it is present to some degree in virtually every topsied case An example of bronchitis of more than usual erity in pulmonary emphysema is shown in Figure 1, in a

section of lung tissue obtained at autopsy. The arrow indicates the lumen of a small bronchus which is filled with exudate containing many polymorphonuclear leukocytes The infectious lesion is largely contained in the bronchus, and the surrounding lung parenchyma shows changes characteristic of emphysema.

Possible Precipitating Factors in Bronchitis

Bronchitis is a regular part of the evolution of illness with the common acute respiratory diseases in the general population It is not usually severe and lasts only a short time Many observers have also noted that one of the common acute respiratory diseases often precedes bronchitis in patients with emphysema, bronchial asthma and other chronic pulmonary diseases, but instead of a benign course, profound disturbances in pulmonary function may result and the illness may be protracted These observations suggest a precipitating role of the common acute respiratory infections in chronic bronchitis and further support for this point of view is obtained when the seasonal incidence of the two diseases is examined

Studies have been made of the frequency of recurrent episodes of bronchitis severe enough to warrant hospitalization in a group of patients with chronic bronchitis by Stuart-Harris and his associates Among 85 patients followed in an outpatient department, hospital admissions for bronchitis and its complications were two to four times more frequent among the winter months, October through March, than in summer Of the total of 101 hospital admissions during the five-year period of observation, 76 per cent occurred in these winter months

The seasonal incidence of the common acute respiratory diseases has been studied by Dingle and his associates in a group of Cleveland families They found there, too, that the incidence of respiratory illness was greatest during the winter season with episodes of infection occurring at an annual rate of six to eight per person per year, in contrast to a rate of approximately three per person per year during the summer months The wives in the households had 5 3 attacks per person-year on the average, and the husbands had rates of 4 1 per person-year. These were young

adults but Von Volkenburgh and Frost in the Hagerstown study have found very little decrease in the frequency of acute respiratory disease among adults in the age range 30 to 60 years Thus is seen a close correlation in the seasonal incidence of the common acute respiratory infections and hospital admissions for recurrent bronchitis Although admittedly this association is not proof of a relationship between these illnesses, it fits well with the clinical observations of many physicians that acute respiratory infections often precede and appear to precipitate attacks of bronchitis

Should these diseases be a factor in initiating bronchitis, then its prevention would depend upon prevention or prompt treatment of the common acute respiratory diseases In this connection it is of great interest to review some of the studies on the etiology of the common acute respiratory diseases They may be summarized briefly as follows In Table 2 are shown the diagnostic categories of the acute respiratory diseases These were taken from the Cleveland study by Dingle and his co-workers and are representative of those of other groups of investigators

Among the six diagnostic categories listed, only two, streptococcal pharyngitis and bacterial pneumonia, are of bacterial etiology and they account for only 2 5 per cent of the total cases which occurred in this large, carefully conducted, three-year study Among the other diseases, influenza and the common cold

TABLE 12 2

Cleveland family study (Dingle and associates)
Number and percentage of respiratory illnesses according to diagnosis, 1948–1950

Diagnosis	Total Infections 3 Year Period	Per Cent of Total
Common respiratory diseases*	4200	94 9
Streptococcal tonsillitis and pharyngitis	107	2 4
Nonstreptococcal exudative tonsillitis and pharyngitis	72	1 6
Primary atypical pneumonia	29	0 7
Pneumococcal pneumonia	3	0 1
Influenza	17	0 4

* The common cold accounted for approximately 60 per cent of these illnesses and the other 40 per cent were made up of the varied acute respiratory illnesses of the undifferentiated type (see text for further explanation)

have been known to have a viral etiology for many years In the remaining three categories (nonstreptococcal exudative pharyngitis and tonsillitis, primary atypical pneumonia, and undifferentiated acute respiratory disease) which account for approximately 40 per cent of cases, a viral etiology has long been suspected Recently a group of viral agents has been isolated independently by Huebner and his associates and by Hilleman and his co-workers which appears to be the cause of these diseases In Huebner's report they were called APC viruses because of their isolation from adenoid tissue, pharynx, and conjunctiva of various persons They have been designated ARD viruses by Hilleman and his associates on the basis of their isolation from patients with acute respiratory disease (ARD). Thus, almost all of the common acute respiratory infections appear to be of viral origin On a theoretical basis, it would not be anticipated that any of the available antimicrobial drugs would prove useful in the prevention or treatment of these viral diseases since, with the exception of the large particle, lymphogranuloma-psittacosis viruses, no active antiviral compounds are known. Furthermore, in a practical way, except for isolated reports of effectiveness of antibiotics in primary atypical pneumonia (Meiklejohn and Shragg), and an apparent reduction in nonbacterial acute respiratory disease in an epidemic following treatment with sulfadiazine (Gezan and associates), there is little encouragement for the prevention or treatment of these diseases with antimicrobial drugs It has been suggested that such beneficial effects as have been observed have derived from the effect of the drugs on associated bacterial pathogens in the treated patients The subject will be considered further in a subsequent part of this report.

The implications from these reports seem to be that the common acute respiratory infections may be responsible for initiating recurrent episodes of bronchitis in patients with chronic pulmonary emphysema, and that present prospects for prevention or treatment of these predominantly viral diseases are not very good Therefore, if these inferences are correct, any measure of control of bronchitis in patients with chronic pulmonary emphysema will depend upon the degree to which bacterial pathogens complicate

bronchitis and the extent to which their treatment with antimicrobial drugs is beneficial

The Role of Bacteria in Chronic Bronchitis

It is the opinion of many investigators that certain bacterial species may be responsible for much of the important symptomatology of chronic bronchitis These species in order of their importance in several published reports are *Hemophilus influenzae* (unencapsulated strains and parainfluenza bacillus), the pneumococci, *Staphylococcus aureus*, and *Klebsiella pneumoniae* (Friedlander's bacillus) Moreover, following treatment with antimicrobial drugs it is frequently observed that coliforms and other gram-negative bacilli, and occasionally *Candida albicans*, are cultured from sputum The role of these microorganisms in the course of infection is occasionally uncertain, but a number of observers believe that they, too, cause bronchitis, especially if the microbial population is very large *Streptococcus viridans*, nonhemolytic streptococci, *Neisseria catarrhalis*, and Corynebacteria species may appear in cultures fairly regularly, but these are generally considered to be saprophytes, although Lepper and his colleagues have implicated *Streptococcus viridans* as a participant in pulmonary infection of patients with severe disability from poliomyelitis who have functioning tracheotomies

The designation of pathogenicity is based on somewhat indecisive criteria Mulder and his colleagues have described unencapsulated *Hemophilus influenzae* as pathogenic on the basis of the presence of the organism in the sputum of patients with bronchitis before treatment, and clinical improvement with reduction in volume and purulence of the sputum and disappearance of *H influenzae* from cultures during treatment with antimicrobial drugs such as penicillin and streptomycin, or chloramphenicol. Similar criteria are described for pathogenicity of the species listed before as potentially pathogenic by several authors (Whitfield, Stuart-Harris and associates, Barach)

This concept is supported by the investigation of May who compared the bacterial flora of specimens of sputum which were mucoid or purulent in character. His material was obtained from

patients with bronchitis In earlier studies he had detected inconsistencies in the results of sputum cultures in cases of bronchitis which resulted from an irregular distribution of bacteria in the sputum. For that reason, in the study referred to he devised a method of multiple cultures from each specimen, in which areas for culture were determined by random selection. He also carefully rinsed sputum specimens in sterile saline in order to minimize the possibility of contamination from nasopharyngeal flora. After treating a large number of specimens in this way he found potentially pathogenic bacteria (*H influenzae*, pneumococci, *Staphylococcus aureus*, and *K pneumoniae*) in 90 per cent of purulent sputa and in only 54 per cent of mucoid sputa. His studies further indicated that there was an irregular distribution of potentially pathogenic and nonpathogenic bacteria in sputum, and that at least five cultures from randomly selected areas of each specimen were required before representative samples of flora were obtained.

Stuart-Harris and his co-workers have pointed out that pneumococci occur in the sputum of patients with bronchitis in about the same frequency as in cultures of the nasopharynx of normal persons In both groups they were about equally distributed among low, intermediate, and high-numbered types of pneumococci This is in contrast to the situation in pneumococcal pneumonia, in which approximately three-fourths of cases are caused by pneumococci of types I to VIII On the basis of these studies they reasoned that the pneumococci in the bronchi in bronchitis are probably derived from the adjacent nasopharyngeal flora as a consequence of interference by the disease with the action of the ciliated bronchial epithelium and other mechanisms which keep the normal respiratory tract virtually free of bacteria In their work the special methods required for cultivating the more fastidious strains of *H influenzae* were not employed. On the basis of Mulder and his associates' observations, however, that unencapsulated strains of *H. influenzae* were found in 84 per cent of patients with chronic bronchitis, and the finding in throat cultures of normal persons (Commission on Acute Respira-

tory Diseases, Straker and associates) of similar high percentages of the same kind of bacteria, it is logical to suggest that these organisms, when present in bronchitis, are probably also derived from the usually saprophytic flora of the nearby nasopharynx. Similarly, an examination of the frequency of occurrence of Friedlander's bacilli and *S. aureus* strains in throat cultures of normal persons reveals in both a low percentage occurrence (less than 10 per cent)* (Straker and associates), a finding which corresponds to the incidence rate of bronchitis with these organisms (Stuart-Harris and associates).

In Stuart-Harris' and his associates' studies, there was concern that mechanical contamination of sputum in passage through the nasopharynx may have occurred. Subsequent observations (Brown and associates) were made, however, in which bronchial aspirates, sputum specimens, and nasopharyngeal cultures from the same patients were compared, and the evidence suggested that mechanical contamination of sputum specimens did not occur significantly in passage through the nasopharynx.

The foregoing evidence, although not constituting proof that the bacterial flora of the bronchi in bronchitis have been endogenously derived from the nasopharynx, nevertheless suggests it so strongly that definitive studies of the pathogenic agents responsible for bronchitis must take cognizance of this possibility.

Mulder and his associates reemphasized that secondary infection with unencapsulated strains of *H. influenzae* may follow infection with influenza virus, measles, and pertussis, and that it would be difficult to exclude a primary infection with a bronchotropic virus in cases of apparent primary *H. influenzae* bronchitis. They felt that the answer to this problem lay with the detection of virus infection in the bronchial epithelium in cases of bronchitis associated with *H. influenzae*. Based on techniques presently available they were unable to discover any alterations in the bronchial epithelium suggesting primary viral infection except in the few cases when influenza viral infection had been identified.

* In recent studies by the authors only 7.5 per cent of almost 2500 throat cultures were positive for *Staphylococcus aureus* (*Micrococcus pyogenes* var. *aureus*).

TABLE 12 3

Antimicrobial therapy of chronic bronchitis associated with Hemophilus influenza (Mulder and associates)

Number of Patients	Treatment	Disappearance of Sputum *H influenzae* not Growing	Reduced Quantity Mucopurulent Sputum *H influenzae* not Growing	Sputum Remains Purulent *H influenzae* Growing
		per cent	*per cent*	*per cent*
15	Penicillin aerosol	20		80
18	Intramuscular penicillin	61	28	11
8	Streptomycin (aerosol and injection)	63		37
92	Penicillin and streptomycin, both by intramuscular injection	80	5	15
24	Chloramphenicol	83*		17
6	Sulfonamides			100

* Relapse in six patients within 1 to 2 weeks Initial treatment for 5 to 10 days.

It was their conclusion that it is probable that *H. influenzae may be a primary cause of bronchitis*

Before this hypothesis can be accepted, however, study will be required of the possible relationship of the ARD (or APC) viruses to chronic bronchitis These viral agents may well produce lesions in the respiratory tract which have escaped detection and strong epidemiologic evidence previously presented suggests that they may play an important role in this disease

Mulder and his associates felt that clinical improvement during *treatment or disappearance of H influenzae and change from* purulent to mucoid sputum, was sound evidence of participation of these bacteria in the bronchitis, either as a primary infection, *or as a secondary invader from the nasopharynx* Such a chain of events has occurred often in his and others' experience. Illustrative of the effect of antimicrobial therapy in patients with chronic bronchitis associated with *H. influenzae* and other bacteria are the clinical reports which follow.

ANTIMICROBIAL THERAPY IN CHRONIC BRONCHITIS

Effect

Mulder and his colleagues have reported observations with various regimens in the treatment of 163 cases of bronchitis as-

sociated with *H influenzae* in the sputum Their criteria of improvement were those described above and a summary of this experience is presented in Table 3

In a group of 15 cases treated with small doses of aerosol penicillin improvement occurred in only 20 per cent By the intramuscular route with doses of penicillin as high as four million units daily, however, improvement was observed in 61 per cent of 18 cases Similar good results were achieved with streptomycin alone, but greater and more permanent benefit was observed when these two agents were combined in treatment (streptomycin 2 0 grams per day, penicillin up to four million units per day) Chloramphenicol was highly effective immediately (83 per cent of cases) but 25 per cent of the total group relapsed in a few days with positive cultures for *H. influenzae* The tetracycline derivatives were also found to be effective by those investigators in a small series of cases

Garthwaite and Barach reported the results of administering 24 courses of treatment to 16 patients with chronic bronchitis The principal organisms cultured from the sputum before treatment were pneumococci, beta-hemolytic streptococci, *S aureus*, and, on two occasions, strains of *H influenzae* One episode was associated with Proteus bacilli in the sputum Following treatment with aerosol, oral or intramuscular penicillin, "marked improvement" occurred on 12 occasions, "moderate" in 8, and "slight" or "none" in 4 Cases with slight or no improvement were not characterized by a predominance of cultures of any one bacterial species A most interesting finding in the study was the appearance in post treatment cultures of gram-negative bacteria, predominantly the coli-aerogenes group, on 13 occasions (53 per cent)

Choice of Agents

From the previous reports it is apparent that a number of different kinds of bacteria may be associated with purulent sputum and other evidences of acute or chronic bronchitis Appropriate therapy may often be selected from a knowledge of the predominant flora of the sputum, in some cases individual antimicrobial susceptibility tests may be needed

TABLE 12 4

In vitro susceptibility to antimicrobial drugs of bacteria potentially pathogenic in chronic bronchitis

Organism		Penicillin	Streptomycin	One or More Tetracycline	Chloramphenicol	Reference
		µg/ml	µg/ml	µg/ml	µg/ml	
Hemophilus influenzae	Range	0 2-6 3*	0 2-6 3*	0 4-12 5*	0 25-3 0†	*Finland
	Mean	± 4	1 6	1 6	—	†*Mulder*
	No of strains	120	150	120	72	
Pneumococci	Range	0 005-0 08	6 2-200	0 2-6 3	0 2-6 3	
	Median	0 01	25	0 8	3 1	*Jackson*
	No of strains	313	84	139	65	
Klebsiella pneumoniae (Friedlander's bacillus)		>5 0*	1-20*	±3 0†	±6 0†	*Dowling †*Knight* (A)

In Table 4 is shown the general pattern of susceptibility of three species of bacteria regarded as potentially pathogenic in chronic bronchitis It may be seen that penicillin, streptomycin, *the tetracyclines, and chloramphenicol are all significantly active* against *H influenzae.* No one regimen has as yet been generally accepted, although the combination of penicillin and streptomycin was very successful in Mulder and his associates' studies Bacteriologic *relapses were described after chloramphenicol, but both it* and the tetracycline derivatives were immediately effective In our own experience the addition of streptomycin to the tetracyclines or chloramphenicol has proved especially useful against many *kinds of infection with* gram-negative *bacilli, including H.* [illegible]

[illegible]

other species With the exception of *low doses of* aerosol *penicillin,* selection of treatments among the regimens listed in the table for infections with *H influenzae* may depend more upon possible

risks of oral intolerance, hypersensitivity, or other untoward effects, rather than any important difference in the antimicrobial effect Aerosol penicillin was not effective in the treatment of H influenzae infections (Table 3)

Pneumococci of all types, so far as is known, are invariably highly susceptible *in vitro* to penicillin, the tetracyclines, chloramphenicol, and erythromycin as indicated in Table 4 These data have been assembled from studies by Finland, Mulder and associates, Jackson and associates, Dowling, and Knight (A) Furthermore, these agents have proved highly effective in treatment Streptomycin is only moderately active against pneumococci and is not used in treatment of this infection

K pneumoniae (Friedlander's bacillus) is best-known as a cause of severe and frequently fatal necrotizing pneumonia In addition, it is not infrequently found in the throat or sputum of patients with bronchiectasis as an apparent saprophyte These bacilli are usually susceptible to the tetracyclines, chloramphenicol, and streptomycin *in vitro*, and examples of this high activity may be seen in Table 4 Penicillin is only slightly active against *K pneumoniae in vitro* and is not effective in treatment of *K pneumoniae* infection.

The problem of handling patients with this organism in their sputum and signs of pulmonary infection is to decide whether or not there is pneumonia developing or merely the more discrete and benign bronchitis Cases of this sort should be treated as though they had pneumonia for a few days until the evaluation is complete Regimens which have been tried by several investigators with some success for *K pneumoniae* are, (1) a combination of streptomycin and sulfadiazine, (2) one of the tetracyclines alone, or in combination with streptomycin, (3) chloramphenicol alone, or with streptomycin The clinical variability of these cases is so great and their occurrence so infrequent that information to determine the relative efficacy of these regimens is not yet available Probably no very important differences exist from the point of view of antimicrobial therapy, although many clinicians prefer the combinations of antibiotics over the regimen including

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TABLE 12 5

Susceptibility of 647 strains of Staphylococcus aureus from hospital patients to antimicrobial drugs, Nashville, 1955

	Penicillin	Tetracycline	Streptomycin	Chloramphenicol	Erythromycin
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Susceptible*	20	48	3	8	92
Intermediate†	21	2	45	91	6
Resistant‡	58	51	52	1	2

* Inhibited by 0 1 μg/ml penicillin, 6 3 μg/ml tetracycline, streptomycin, chloramphenicol, 1 2 μg/ml erythromycin

† Inhibited by 1 0 μg/ml penicillin, 25 μg/ml tetracycline, streptomycin, chloramphenicol, and erythromycin

‡ Not inhibited by 1 0 μg/ml penicillin, 25 μg/ml of remaining agents

the sulfonamides If bronchitis only is present, a combination of antibiotics in treatment is probably unnecessary, and treatment with one of the tetracyclines or chloramphenicol may be satisfactory

Staphylococci have become increasingly resistant in recent years to several antimicrobial drugs in frequent clinical use This phenomenon has been most apparent in staphylococci obtained from hospital patients and much less so among cultures from the general population In Table 5 is shown the susceptibility of 647 strains of staphylococci obtained from the respiratory tract of hospital patients in Nashville in 1955 (Knight, B) It may be seen that one fifth or less are susceptible to penicillin and streptomycin with a half or more of strains falling into the resistant category A larger proportion is susceptible to tetracycline (and its other derivatives) while a majority fall into the intermediate category of effect to chloramphenicol. Although these *in vitro* susceptibilities to chloramphenicol are not impressively great, they are in a range of drug concentration which is easily obtained in the serum with usual therapeutic doses Erythromycin, one of the most recently introduced antibiotics, is highly active against a large majority of staphylococci obtained from hospital patients or from the general population

From the table one can see that the greatest activity against

staphylococci *in vitro* was exhibited by erythromycin, chloramphenicol, the tetracyclines, penicillin, and streptomycin in that order. In treatment of staphylococcus infection selection of agents should be based on known or expected high *in vitro* susceptibility of the organism, but treatment with such agents may not always be successful since studies have shown that the use of either penicillin or the tetracyclines in cases with drug-susceptible strains may be followed in hospital practice by the acquisition of strains resistant to both drugs (Knight and Holzer). Furthermore, these staphylococci are usually also resistant to streptomycin. Such multiple drug-resistant staphylococci are often referred to as nosocomial or "hospital" staphylococci. For this reason many infections with staphylococci in hospitals are now treated with combinations which include chloramphenicol and erythromycin. None of these regimens is invariably successful, and in severe cases several drug combinations may be tried before success or failure of the treatment ensues. In the treatment of patients outside the hospital there is a greater possibility of encountering strains of staphylococci which are susceptible to penicillin and the tetracyclines. For that reason these agents may be used more successfully in home treatment.

It was pointed out earlier in Barach's studies that members of the coli-aerogenes group of bacteria frequently are cultured from the sputum or throat following treatment with penicillin. Mulder and associates have described this in their studies and have reported that these organisms may be present under very benign conditions without purulent sputum or symptoms of bronchitis. They are not invariably benign, however, and following treatment with streptomycin, the tetracyclines, and chloramphenicol, the gram-negative bacteria may achieve predominance. Proteus species and *Pseudomonas aeruginosa* may appear and be associated with severe purulent bronchitis. Many observers have described these occurrences following treatment of acute bacterial pneumonia and other respiratory infections and the name "superinfections" has been applied to them.

The gram-negative bacilli are among the least susceptible to

TABLE 12 5

Susceptibility of 647 strains of Staphylococcus aureus from hospital patients to antimicrobial drugs, Nashville, 1955

	Penicillin	Tetracycline	Streptomycin	Chloramphenicol	Erythromycin
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
Susceptible*	20	48	3	8	92
Intermediate†	21	2	45	91	6
Resistant‡	58	51	52	1	2

* Inhibited by 0 1 μg /ml penicillin, 6 3 μg /ml. tetracycline, streptomycin, chloramphenicol, 1 2 μg /ml erythromycin

† Inhibited by 1 0 μg /ml penicillin, 25 μg /ml. tetracycline, streptomycin, chloramphenicol, and erythromycin

‡ Not inhibited by 1 0 μg /ml penicillin, 25 μg /ml of remaining agents.

the sulfonamides. If bronchitis only is present, a combination of antibiotics in treatment is probably unnecessary, and treatment with one of the tetracyclines or chloramphenicol may be satisfactory

Staphylococci have become increasingly resistant in recent years to several antimicrobial drugs in frequent clinical use This phenomenon has been most apparent in staphylococci obtained from hospital patients and much less so among cultures from the general population In Table 5 is shown the susceptibility of 647 strains of staphylococci obtained from the respiratory tract of hospital patients in Nashville in 1955 (Knight, B) It may be seen that one-fifth or less are susceptible to penicillin and streptomycin with a half or more of strains falling into the resistant category A larger proportion is susceptible to tetracycline (and its other derivatives) while a majority fall into the intermediate category of effect to chloramphenicol Although these *in vitro* susceptibilities to chloramphenicol are not impressively great, they are in a range of drug concentration which is easily obtained in the serum with usual therapeutic doses. Erythromycin, one of the most recently introduced antibiotics, is highly active against a large majority of staphylococci obtained from hospital patients or from the general population

From the table one can see that the greatest activity against

staphylococci *in vitro* was exhibited by erythromycin, chloramphenicol, the tetracyclines, penicillin, and streptomycin in that order In treatment of staphylococcus infection selection of agents should be based on known or expected high *in vitro* susceptibility of the organism, but treatment with such agents may not always be successful since studies have shown that the use of either penicillin or the tetracyclines in cases with drug-susceptible strains may be followed in hospital practice by the acquisition of strains resistant to both drugs (Knight and Holzer) Furthermore, these staphylococci are usually also resistant to streptomycin Such multiple drug resistant staphylococci are often referred to as nosocomial or "hospital" staphylococci For this reason many infections with staphylococci in hospitals are now treated with combinations which include chloramphenicol and erythromycin None of these regimens is invariably successful, and in severe cases several drug combinations may be tried before success or failure of the treatment ensues In the treatment of patients outside the hospital there is a greater possibility of encountering strains of staphylococci which are susceptible to penicillin and the tetracyclines For that reason these agents may be used more successfully in home treatment

It was pointed out earlier in Barach's studies that members of the coli-aerogenes group of bacteria frequently are cultured from the sputum or throat following treatment with penicillin Mulder and associates have described this in their studies and have reported that these organisms may be present under very benign conditions without purulent sputum or symptoms of bronchitis They are not invariably benign, however, and following treatment with streptomycin, the tetracyclines, and chloramphenicol, the gram-negative bacteria may achieve predominance Proteus species and *Pseudomonas aeruginosa* may appear and be associated with severe purulent bronchitis Many observers have described these occurrences following treatment of acute bacterial pneumonia and other respiratory infections and the name "superinfections" has been applied to them

The gram-negative bacilli are among the least susceptible to

antimicrobial drugs of all the bacteria which may be associated with respiratory infection In Figure 2 is shown the antimicrobial spectrum of the common gram-negative bacteria obtained from recent studies (Horton and Knight) The filter paper disk susceptibility test which is routinely used in many hospitals was employed and the results are reported as "susceptible," "moderately susceptible," "moderately resistant" and "resistant". Thirty to 250 strains were tested against each drug for each year. In the two years described there is no suggestion of an increase in resistance of gram-negative bacilli to the antimicrobial drugs studied. The *Escherichia coli* and *Acrobacter aerogenes* strains exhibit very similar patterns of susceptibility as might be anticipated from their close biologic relationship. By far the highest degree of activity against the coli-aerogenes group was exhibited by chloramphenicol, followed by the tetracyclines, polymyxin, and streptomycin

The only agent of significant activity against *Pseudomonas aeruginosa* cultures was polymyxin B with some inhibitory effect shown by chloramphenicol The Proteus sp were in somewhat of a contrast to Pseudomonas strains with little effect shown by polymyxin B, although chloramphenicol and streptomycin showed some activity

Based on clinical experience, it is the authors' opinion that the agents described as highly effective *in vitro* may be the most effective in treatment In addition, it has been found that definitely beneficial results may follow clinical use of the tetracycline derivatives when only moderate degrees of *in vitro* activity are shown Furthermore, it is a not very unique experience to discover that none of the agents presently available influences to an important extent infections caused by Proteus or Pseudomonas. In this situation temporary discontinuation of antimicrobial treatment may prove beneficial and on occasion combinations of active agents may be effective when a single drug is not

Another microorganism which may cause troublesome superinfection is the yeast, *Candida albicans* It appears in sputum cultures more often than it apparently causes respiratory infection Nevertheless, in patients with chronic bronchitis, pulmonary

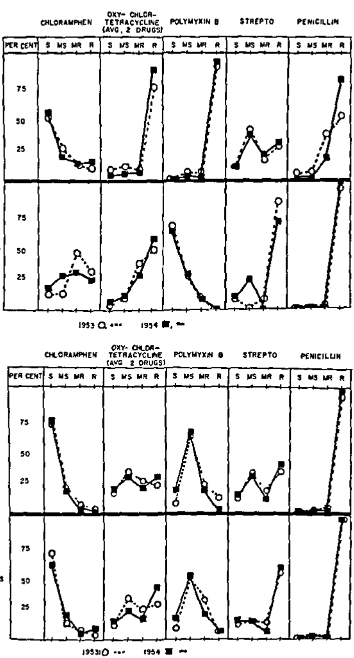

FIG 12 2 Patterns of antimicrobial susceptibility of recent isolates of common gram-negative bacilli Paper disk method of testing (From Horton and Knight, with permission.)

TABLE 12.6

Commonly used dosage schedules of antimicrobial drugs in chronic bronchitis and other respiratory infections

Drug and Dose (for Average-Sized Adult, est. 70 Kg.)

Penicillin
- Aqueous procaine penicillin 600,000 units every 12 hours intramuscularly, with or without probenecid 1.5 to 2.0 gm. per day by mouth
- Penicillin G or V oral preparations, 1,000,000 units 2 or 3 times daily.*
- Aerosol penicillin (see text)

Chlortetracycline (Aureomycin), oxytetracycline (Terramycin), or tetracycline
- One-half gm. every 4 or 6 hours by mouth. In long continued therapy 0.5 gm. one or two times daily may suffice

Chloramphenicol (Chloromycetin)
- One and one-half to 4 grams daily by mouth. Microcrystalline powder in suspension may be given intramuscularly effectively in the same dosage

Streptomycin or dihydrostreptomycin, or mixture of equal parts of each
- One and one half or 2.0 gm. daily in divided intramuscular doses

Erythromycin
- One to 1.5 gm. in divided oral doses daily. Lower maintenance doses may suffice

Polymyxin B
- Two and one-half to 3 mg. per Kg. of body weight per day in divided doses by intramuscular injection. *Caution:* nephrotoxic, observe for oliguria, *proteinuria and abnormal urinary sediment*

Bacitracin
- Do not exceed 100,000 units daily by intramuscular injection in divided doses

Nystatin
- Two and one-half million units in divided oral doses each day

* *Oral penicillin preparations result in fewer sensitivity reactions than injected* penicillin and are thus often preferred in long-term treatments

neoplasia, bronchiectasis, and other respiratory diseases, purulent sputum may appear particularly following long courses of antimicrobial therapy in which a predominant growth of *C. albicans* may be detected. None of the agents previously described is effective against this organism, but recently a new drug, nystatin, has been found to be of benefit in human Candida infections in various parts of the body, although in severe long-standing infections the response may be slow and incomplete.

In Table 6 are listed dosage regimens of the antimicrobial drugs described in the foregoing section which may be used in treating acute and chronic pulmonary infections.

Penicillin by Aerosol

The apparent advantage of penicillin administered by this route depends on the fact that very high sputum concentrations may be attained For example, Barach and Garthwaite reported a mean value of 461 units per ml of sputum in a series of patients following administration of 50,000 unit doses by aerosol. In contrast, sputum concentration following 50,000 unit doses intramuscularly were so low that they could not be measured Although penicillin is absorbed into the serum after aerosol administration it occurs to a lesser extent than after parenteral forms of treatment

It was found that the highest sputum concentrations were achieved by using an aerosol in which the particle sizes of penicillin ranged from 0 5 to 2 5 μ Larger particles were removed in the chamber of the machine or were sedimented out in the nasopharynx or trachea, and smaller particles were presumably carried to the alveoli where they were promptly absorbed into the blood stream, and in either case did not contribute to the sputum concentration A number of observers have raised the point that penicillin by aerosol may not penetrate well into areas of bronchiectasis and associated atelectasis where the most important infectious lesions are located No studies are presently available on this question Clinical results with aerosol penicillin therapy have been sufficiently good to justify its continued use, however, and it is hoped that further studies of the distribution of aerosolized penicillin and other agents in the lung will be made A commercially available device which is suitable for aerosol administration of penicillin has been constructed on Barach and his co-workers' design * It is suitable for home or hospital use

In the Chest Clinic at Vanderbilt University Hospital† an important part of treatment of infection complicating various kinds of chronic pulmonary diseases among outpatients is built around

* Vapocillin rehreathing apparatus, Vaponeprin Company, Upper Darby, Pennsylvania

† This treatment was developed by Dr Hollis E Johnson, Director, Dr. Clarence Woodcock, and others of the visiting staff of the Chest Clinic, Vanderbilt University Hospital

aerosol administration of penicillin and streptomycin. This is representative of a fairly general trend in the treatment of these diseases in many clinics and the results are considered to be highly successful For that reason, an outline of these procedures is presented in Table 7.

Duration of Antimicrobial Therapy in Chronic Bronchitis and Other Pulmonary Infections

CHRONIC BRONCHITIS

In patients who do not respond to treatment and who have continued production of purulent sputum and other signs of infection, one to two weeks constitutes an adequate test of the drug's effect and thereafter it should be discontinued. When clearing of sputum and other improvement occurs, treatment should be continued for a period long enough for healing of the damaged bronchi to take place There is no sure way to determine this, but generally three to six weeks of treatment are sufficient Dosages may be reduced after initial control is established Discontinuing treatment for short periods may help to decide when it is safe to cease treatment permanently

BRONCHIECTASIS

Special problems are present in the treatment of bronchiectasis because of the fixed, dilated and scarred bronchi with pooling and stagnation of exudate Antimicrobial therapy alone may not be successful and Barach has pointed out the folly of expecting good results from antimicrobial treatment in the presence of a large volume of purulent secretion in a bronchiectatic cavity. Occasionally bronchiectasis is present but unsuspected in other chronic pulmonary diseases The production of large volumes of foul sputum should lead to suspicion of its presence and measures to drain these collections of pus are necessary

Postural drainage, bronchoscopy, mechanical exsufflation may each be effective at times in doing this The effects of these procedures may be improved by administration of bronchodilators such as ephedrine, aminophylline, racemic epinephrine (Vapone-

TABLE 12 7

Aerosol treatment for outpatients of infections complicating chronic pulmonary diseases

Chest Clinic, Vanderbilt University Hospital

Penicillin aerosol Prepare a dose by adding one 50,000 unit tablet of soluble penicillin to 8 drops of water (about ½ ml) Alternatively, the penicillin tablet may be added to 8 drops of ¼ per cent neosynephrine solution or 8 drops of streptomycin solution (see below), or 8 drops of water containing both neosynephrine and streptomycin

Streptomycin aerosol Prepare by adding 10 ml of water to 1 gm of streptomycin or dihydrostreptomycin sulfate A dose is 8 drops or approximately 50 mg of streptomycin

Nebulizers Devilbiss* glass or plastic nebulizers, or the device previously described which was devised by Barach and associates, is usually prescribed

Expectorants Ten to 20 drops of saturated solution of potassium iodide per dose This amount should be reached only after several days of increasing dosage to avoid untoward reactions Water 400 ml , by mouth, per dose

Procedure One hour before each meal and before bedtime a dose of each expectorant is taken (potassium iodide and water) After 45 minutes postural drainage is performed for one to two minutes accompanied by vigorous coughing Then, following maximal expiration, deep inspiration is accompanied by three hard squeezes on bulb of nebulizer with the device in position in mouth Inhalations are repeated until the dose is exhausted which usually requires 15 to 20 minutes

Neosynephrine is used to counteract the irritating effect of the antibiotic mist in the presence of asthmatic symptoms or acute bronchitis Streptomycin is added in cases infected with *H influenzae* or those which are unresponsive to penicillin alone Postural drainage is especially beneficial in cases of bronchiectasis

A sulfonamide, a tetracycline derivative, chloramphenicol, or erythromycin may be used orally or parenterally, to supplement aerosol treatment when indicated These agents are not usually administered by aerosol in this clinic

* Devilbiss glass nebulizer, model no 40, or Devilbiss plastic nebulizer, model no 41

frin), isopropyl adrenalin (Isuprel), and other compounds Further descriptions of these compounds and their use will be found in another part of this volume It is Barach's experience that almost continuous treatment of patients with bronchiectasis with penicillin or other agents may be required to keep the volume of the sputum low and to keep it relatively free of pus This is somewhat in contrast to the situation with bronchitis, otherwise the principles of management are applicable which have been described earlier

PNEUMONIA

Bacterial pneumonia caused by several of the organisms previously described may complicate the course of chronic bronchitis and pulmonary emphysema The therapeutic approach should follow that outlined for the other kinds of bacterial infections of the lung

ROLE OF BACTERIA IN SPUTUM WITHOUT PURULENCE

Throughout this report it has been emphasized that the diagnosis of a functioning role of bacteria in chronic bronchitis and other pulmonary disease depends upon the finding of the organisms in large numbers in purulent sputum Thus an important part of the diagnosis is the examination of the stained smear of the sputum Organisms and leukocytes can be visualized and often the correct identification of the predominant bacterial flora can be made from the smear Culture is a necessary concomitant, however, and with these two procedures continuous effective scrutiny of the course and therapy of patients may be maintained.

Not infrequently patients with emphysema may have cough, some signs of pulmonary insufficiency and produce small amounts of mucoid sputum Culture will often reveal a mixed flora including *Neisseria catarrhalis*, *Streptococcus viridans*, nonhemolytic streptococci, as well as some of the strains previously described as potentially pathogenic These findings do not fulfill the criteria set forth above for the diagnosis of infectious bronchitis, and antimicrobial treatment is not usually followed by any definite improvement

PREVENTION OF CHRONIC BRONCHITIS AND OTHER CHRONIC PULMONARY DISEASES BY ANTIMICROBIAL THERAPY

Data were presented earlier in this report which suggested that the predominantly viral-caused common upper respiratory infections may be important in initiating recurrent episodes of bronchitis and infection in emphysema At present, there is no satisfactory evidence that available antimicrobial agents are active against the viruses which cause or are suspected to cause

these infections Based on this concept, it would appear that present prospects for prevention of the common upper respiratory infections and any consequent provocative effects they may exert in causing bronchitis, are not favorable

Prevention or early alleviation of severity of bacterial infections of the respiratory tract, however, offers a much more favorable possibility of benefit, whether they arise following virus infections or occur independently Many physicians caring for patients with chronic pulmonary disease at present almost routinely employ some kind of antimicrobial therapy on a semicontinuous regimen, especially during winter months There is considerable unanimity that such measures are beneficial Few formal studies have been reported on this subject, but one which is of interest is that of McVay and Sprunt In a small series of older persons treated as outpatients for several months, they found a considerable reduction in incidence of respiratory infections among those who received 0 5 gram of chlortetracycline daily by mouth in comparison to a small group of untreated patients In the treated patients sedimentation rates were generally lower and hematocrit and body weight increased during treatment They found few evidences of intolerance to this regimen and no increase in drug resistance of staphylococci cultured during treatment The authors felt that the administration of chlortetracycline was beneficial The lack of appearance of chlortetracycline-resistant staphylococci during treatment is a distinctly favorable omen for future preventive efforts Finke has reported similar beneficial results in long term therapy with penicillin in patients with bronchitis

In general, it is considered to be of importance by the authors that antimicrobial prophylaxis will best be administered on an outpatient basis in order to avoid exposure to drug-resistant staphylococci and possibly other drug-resistant infectious agents present in hospital populations The dose employed should be the lowest that will provide a significantly beneficial effect and it may well be that outpatient care and low doses of drug are the basis for the failure of drug resistant staphylococci to appear in McVay and Sprunt's study Drugs should be given by mouth

when possible because of the lower rate of sensitivity reactions by this route Aerosol therapy, particularly in bronchiectasis, may prove useful when other routes of administration are unsuccessful Treatment periods should be interrupted from time to time to allow reestablishment of normal saprophytic flora in the hope that *superinfections may be avoided.*

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Chapter 13

THE DIFFUSING CAPACITY OF THE LUNGS IN PATIENTS WITH PULMONARY EMPHYSEMA

RICHARD L. RILEY, M.D.

In 1909 Christian Bohr expounded the physical principles involved in the determination of the diffusing capacity of the lungs and thereby gave theory a commanding lead over practice. Even after 46 years of intermittent efforts to devise practical methods there are still valid reservations regarding the accuracy and physiologic interpretation of values for diffusing capacity obtained in the study of patients with emphysema. In spite of such reservations, it appears, at least to the writer, that there is now a sufficient body of reasonably well confirmed observations to make the diffusing capacity an appropriate subject for inclusion in a comprehensive discussion of emphysema. It will become apparent, however, that theory has not stood still while practice caught up, and that conclusive demonstration of many of the ideas to be presented remains for the future.

A great controversy raged at the time of Christian Bohr regarding the secretion of oxygen by the lungs. This stimulated intensive efforts to devise methods for assessing alveolo-capillary diffusion in order to ascertain whether the process of diffusion was adequate to account for gas exchange or whether oxygen secretion was a necessary additional process in times of need. In 1915 Marie Krogh published both a description of a method for determining diffusing capacity and data strongly suggesting that diffusion alone is adequate to account for gas exchange across the pulmonary membrane. This conclusion has come to be generally accepted.

For 31 years matters stood at this point Then, in 1946, a low oxygen method for determining diffusing capacity was described by Lilienthal, Riley, Proemmel and Franke This was followed by a series of papers on methodology and by attempts to study the diffusing capacity in disease Then Filley, MacIntosh and Wright described a steady-state method for determining the diffusing capacity for carbon monoxide, and Forster, Briscoe and Bates presented an ingenious way to improve on Krogh's single breath method There are at present, therefore, steady-state methods for determining the diffusing capacity for both carbon monoxide and oxygen, as well as single breath methods for determining the diffusing capacity for carbon monoxide. All of these methods have been applied in at least a few cases to the study of the diffusing capacity in patients with emphysema

The diffusing capacity of the lungs for a given gas is the amount of that gas diffusing per minute across the pulmonary membrane divided by the mean difference between the partial pressures of the gas on either side of the membrane It is thus the rate at which the gas would diffuse in response to a constant pressure gradient of 1 mm Hg Customarily the "pulmonary membrane" is considered to be the tissue-fluid barrier which separates the alveolar gas from the hemoglobin molecules in the pulmonary capillary blood In addition to the alveolar membrane and the capillary endothelium, the diffusion pathway therefore includes plasma, red cell wall and substance within the red cell Although work by Roughton and others raises the possibility of separating the diffusion characteristics of the fixed part of the membrane from the circulating portion, this subdivision will not concern us in the present discussion For purposes of comparing patients with normal persons such a subdivision is unnecessary if differences in the fixed part of the membrane account for the major portion of observed differences in diffusing capacity This we believe to be the case

The characteristics of the pulmonary membrane which are important in relation to diffusion are its thickness, its physicochemical properties and its area The thickness determines the length of the diffusion pathway and, other things being equal, the longer

the diffusion pathway, the lower the diffusing capacity The physicochemical properties of the pulmonary membrane depend upon the types of tissue involved, and they determine the ease with which a gas can diffuse through a given thickness of membrane. It is easier, for example, for oxygen to diffuse across a layer of edema fluid than to diffuse across a layer of scar tissue of equal thickness Increase in the thickness of the membrane and alteration in physicochemical properties are likely to occur together when the diffusion pathway is lengthened by the presence of abnormal tissue such as edema fluid, fibrous and collagenous tissue, cellular infiltration, or other material.

The area of the pulmonary membrane is closely related to the area of the walls of the capillaries taking part in gas exchange. In the determination of diffusing capacity, only those capillaries which are perfused with blood and which course through ventilated alveoli are taken into account The remaining capillaries, which are either nonperfused or pass through nonventilated alveoli, represent potential diffusing surface As cardiac output increases in response to exercise, these capillaries become perfused with blood, take part in gas exchange, and contribute to the diffusing capacity of the lung as a whole. The effective area of the pulmonary membrane thus varies in response to physiologic changes Structural changes such as loss of lung tissue by surgical resection or disintegration of alveolar walls in emphysema cause permanent reduction in the area of the pulmonary membrane The problem of distinguishing between the effects on the diffusing capacity of structural changes as opposed by physiologic changes is of particular concern in the present discussion since, if structural factors could be identified as such, the diffusing capacity could be used as a means of quantifying damage to the alveolar walls in emphysema

An approach which has proved helpful in identifying structural damage to the alveolar walls is the determination of the highest value for diffusing capacity which can be achieved under the combined stimulus of physical exercise and hypoxia. The term, maximal diffusing capacity, has been applied to this value be-

cause of the experimental observation that, when determined by the low oxygen method, the diffusing capacity increases with increasing exercise to a maximal value which then cannot be exceeded even though the severity of exercise is further increased. This finding was reported by Riley, Shepard, Cohn, Carroll and Armstrong in 1954 and has not to our knowledge been repeated using the low oxygen method. Partial confirmation, using carbon monoxide methods, has come from the work of Filley, MacIntosh and Wright and of Bates, Boucot and Dormer. The most likely explanation for the phenomenon is that more and more capillaries take part in gas exchange as the cardiac output increases in response to exercise. When the entire capillary bed is perfused, or at least as much of it as can be perfused in response to physiologic stimuli, the area of the diffusing surface can expand no more. The corresponding value for diffusing capacity is therefore maximal, and further increments of blood flow do not cause further increments of diffusing capacity. In the resting state the diffusing capacity defines the diffusional characteristics of an unknown fraction of the pulmonary membrane, and the maximal diffusing capacity defines the characteristics of all the membrane which is available for gas exchange. The maximal diffusing capacity is therefore more closely related to the structural characteristics of the pulmonary membrane as a whole.

Interpretation of the maximal diffusing capacity of a patient in either physiologic or morphologic terms requires comparison with the normal value for a person of the same age and size. Normal standards which can be used for this purpose have been reported by Cohn, Carroll, Armstrong, Shepard and Riley, based upon the study of 21 normal men between the ages of 17 and 76 years. Results of this work are expressed in the equation

$$D_{O_2} = 0.67 \text{ height in cm} - 0.55 \text{ age in years} - 40.9$$

(S.D. = 10 units of diffusing capacity)

It seems unlikely that a patient whose maximal diffusing capacity falls within the normal range can have significant damage to his alveolar walls. If, on the other hand, the maximal diffusing

the diffusion pathway, the lower the diffusin physicochemical properties of the pulmonary m upon the types of tissue involved, and they d with which a gas can diffuse through a given brane It is easier, for example, for oxygen to di of edema fluid than to diffuse across a layer of thickness Increase in the thickness of the m tion in physicochemical properties are likel when the diffusion pathway is lengthened b normal tissue such as edema fluid, fibrous an cellular infiltration, or other material

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Chapter 14

RESPIRATORY ACIDOSIS

REUBEN M CHERNIACK, M D

INTRODUCTION

Respiratory acidosis, an elevation of arterial CO_2 tension due to respiratory insufficiency, is being recognized with increasing frequency in patients with chronic obstructive emphysema The body can tolerate a fall in arterial O_2 tension more readily than a rise in CO_2 tension since the oxyhemoglobin saturation will be little affected until anoxia is fairly severe Although the emphysematous patient may tolerate mild elevation of the CO_2 tension for long periods of time, severe retention of CO_2 leads to the development of a vicious circle with reduction of ventilation, coma and even a fatal termination Increased recognition of this serious condition has led to the development of therapeutic measures which, fortunately, are capable of alleviating the condition

Retention of CO_2 is the consequence of ineffective alveolar ventilation and is always associated with anoxia unless the individual is inhaling oxygen with a partial pressure greater than that in room air Although usually due to diffuse obstructive disease of the airways, as in patients with pulmonary emphysema, it may also be caused by abnormalities of the chest cage, reduction of lung tissue, increased resistance to lung stretching and neuromuscular or skeletomuscular disorders In a patient with pulmonary disease the alveolar ventilation may be sufficient to provide adequate elimination of CO_2 at rest, thus maintaining a normal arterial pCO_2 However, the increased ventilatory demand of exercise or the superimposition of an acute infection or pulmonary congestion may lead to retention of carbon dioxide

Knowledge of the physiologic disturbances associated with carbon dioxide retention will lead to an early recognition of this condition and serve as a guide to its management Respiratory acidosis will therefore be discussed in terms of the pathophysiology, clinical manifestations and management.

Pathophysiology of Respiratory Acidosis

Alveolar Hypoventilation

The normal function of the respiratory system is to supply oxygen to the blood and to regulate the arterial CO_2 tension The volume of air which is moved into and out of the lungs is termed the *ventilation and is expressed in liters per minute At a constant* tidal volume it is equal to the tidal volume times the respiratory rate *The total ventilation per minute is composed of a dead-space component which does not take part in gaseous exchange, and an alveolar component which supplies oxygen to and removes CO_2 from the pulmonary capillary blood*

The dead space component normally consists of the actual dead space of the conducting airways (anatomic dead space) In addition, however, there may be alveoli which, although adequately ventilated, are poorly perfused with blood (dead-space-like ventilation) The "physiologic dead space" represents that part of the ventilation which does not take part in gaseous exchange However, the measurement of physiologic dead space does not differentiate ventilation of the anatomic dead space from that part of the ventilation going to poorly or nonperfused alveoli Any increase of the dead space component will reduce the proportion of the total ventilation being used for gaseous exchange

In emphysema three factors contribute to the alveolar hypoventilation The structural abnormality of the lungs increases the physiologic dead space so that a large portion of each inspiration is wasted in ventilating poorly or nonperfused alveoli, resulting in arterial anoxia and elevation of CO_2 tension

The increased functional residual capacity in emphysema in-

tion to an increased dead space, there is impaired usage of the alveolar component

In addition there is uneven distribution of inspired gas in emphysema indicating poor ventilation of a significant number of alveoli Perfusion of the alveoli which are poorly ventilated results in arterial anoxia as well as a tendency towards CO_2 retention because not enough oxygen is added to, or CO_2 removed from the blood perfusing these alveoli

Initially these disturbances can be overcome by increasing the total ventilation and hyperventilating the remaining well-ventilated, well-perfused alveoli In this way the patient with mild or moderate emphysema is able to maintain a normal CO_2 tension by an increased minute ventilation

The alveolar CO_2 tension is intimately related to and dependent upon the alveolar ventilation For any given level of metabolism and CO_2 production, a change in alveolar ventilation will cause an inverse change in alveolar pCO_2 Since the arterial pCO_2 is virtually identical with the average alveolar pCO_2, a decrease in alveolar ventilation with no change in CO_2 output will result in an increase of arterial pCO_2 Similarly an increased CO_2 production without comparable increase in alveolar ventilation will result in an elevated arterial CO_2 tension Thus it can be seen that there must be a fine regulation of ventilation if the arterial pCO_2 is to be maintained at a normal level Alveolar and arterial pCO_2 do not rise to compensate for a fall in alveolar ventilation but rise as a direct consequence of a reduction of alveolar ventilation

Work of Breathing

When bronchospasm, secretions or edema narrow the air passages, or the lungs are congested, the work of breathing becomes great, and the maximum breathing capacity is frequently grossly reduced, indicating a reduced ventilatory reserve At this stage even the mild increase in ventilation necessary to maintain a normal arterial CO_2 tension at rest may give rise to considerable dyspnea CO_2 retention occurs in the emphysematous subject, when the compensatory increase in ventilation fails to achieve its purpose

Riley has recently stressed the important concept *that an increase in the work of breathing itself adds to the accumulation of CO_2 in the body* Since the body tolerates elevated CO_2 tensions to spare oxygen for nonventilatory work, he has suggested that respiratory acidosis be viewed as an adaptive mechanism. Such a hypothesis had previously been suggested by Cain and Otis who claimed that the body tolerates a rise in CO_2 tension during resistance breathing "in preference to expending the effort that would be required to keep it at the original level" Otis also showed *that with hyperventilation, even in normal individuals, there will be a maximum ventilation beyond which alveolar pCO_2 will not continue to be lowered, but will actually increase with further* increase in ventilation When there is obstructive disease of the bronchi with increased work of breathing the volume of ventilation which would be effective in lowering pCO_2 would be lower than in normals Thus, Donald and Christie and Wilson and associates observed that patients with emphysema are unable to lower their arterial pCO_2 voluntarily, despite increasing the total minute ventilation

It is obvious that anything which increases the work of breathing in emphysema, *whether it be exercise or increased resistance* to respiration due to bronchial obstruction or pulmonary congestion, *will lead to CO_2 retention* Cohn *and associates* demonstrated a rise in arterial CO_2 tension in an emphysematous subject during exercise despite an increased ventilation. If, due to the ventilatory disability, there is a lag in CO_2 excretion on a succession of periods of exercise, there will be a tendency for the pCO_2 to rise and respiratory acidosis to develop The superimposition of pulmonary infection or heart failure in patients with emphysema would also further increase the work of breathing to the point where inadequate ventilation results in an acute elevation of pCO_2

Acid-base Relationships

The respiratory control of acid-base balance is dependent upon variations in the bicarbonate buffer system. Changes in arterial

CO_2 tension affect the arterial pH in a manner indicated by the Henderson-Hasselbalch equation

$$PH = 6.10 + \log \frac{HCO_3^-}{H_2CO_3}$$

Since H_2CO_3 and free CO_2 are in equilibrium and 0.0301 mM of CO_2 will be dissolved in solution for every mm Hg CO_2 tension, the equation becomes

$$pH = 6.10 + \log \frac{HCO_3^-}{0.0301\ pCO_2}$$

The arterial pCO_2 is normally maintained at about 38 mm Hg. Thus the H_2CO_3 content is normally approximately 1.2 mM/liter.

The relationship between HCO_3^- and H_2CO_3 (or 0.0301 pCO_2) is normally maintained at a ratio of 20:1 so that the pH is very close to 7.40. Since the total CO_2 is present as HCO_3^- and H_2CO_3, and the normal CO_2 content is approximately 26 mM/l, the normal HCO_3^- content is approximately 25 mM/liter.

The denominator of the ratio $HCO_3^-/0.0301\ pCO_2$ is controlled by the relationship of CO_2 production to alveolar ventilation. Thus if the alveolar pCO_2 increases due to diminished alveolar ventilation, the ratio of $HCO_3^-/0.0301\ pCO_2$ diminishes, and the arterial pH shifts to the acid side. The numerator of this ratio is controlled predominantly by renal mechanisms and buffers such as hemoglobin.

The physiologic effects of respiratory acidosis are accompanied by an accelerated secretion of hydrogen ion and ammonia by the kidneys. These renal mechanisms result in increased fixed anion excretion and enhanced renal tubular reabsorption of cation, thus raising the plasma buffer anion concentration to higher than normal levels. The resultant plasma picture will be a markedly reduced plasma chloride, an elevated HCO_3^-, and a pH which is nearly normal. The serum sodium is usually normal. In the acute stages serum potassium may be elevated, and in severe cases signs and symptoms of hyperkalemia may develop. This is shown

in Figure 14 3, where it can be seen that with an elevated pCO_2 the plasma chloride was low and potassium high, although the sodium was not affected

As the condition progresses, the HCO_3^- content rises and in fully compensated cases may be at very high levels On the other hand, if this determination is made shortly after the change in ventilation, and before compensatory mechanisms have taken place, the value will be little deviated from normal.

Role of CO_2 and Anoxia in the Regulation of Respiration

In the normal individual respiration is primarily under the control of the medullary respiratory center. The activity of this center is affected by the CO_2 tension and the hydrogen ion concentration of the arterial blood A rise in CO_2 tension or hydrogen ion concentration results in immediate stimulation of this center to increase the minute ventilation and blow off excess CO_2. In contrast the peripheral chemoreceptors in the carotid and aortic bodies are relatively insensitive to changes in arterial pH or CO_2 tension, but are sensitive to a lowering of arterial O_2 tension, causing a prompt increase in pulmonary ventilation

It has been shown that the severely emphysematous subject does not respond to the inhalation of CO_2 by the normal increase in ventilation Donald and Christie also noted a delay in response to CO_2 in some emphysematous subjects and attributed this to delayed mixing of the inspired gas in the lung Although this factor may play a role in the diminished ventilatory response to CO_2 in patients with severe emphysema, it does not explain the entire picture The possibility of acclimatization of the respiratory center to high CO_2 tensions has been suggested by many workers Schafer observed adaptation to a CO_2 environment in normal subjects, and Otis noted an elevated arterial CO_2 and diminished response to CO_2 after exposure to 3 per cent CO_2 for 3 days. Changes in respiratory response to CO_2 in normal subjects who had been overbreathed in a body respirator have also been demonstrated by Brown and associates. It has therefore been postulated that the respiratory mechanism adapts itself to prolonged dis-

turbances of pCO_2 level by changes in the sensitivity of the respiratory center

Although patients with emphysema may have developed some acclimatization to higher pressures of CO_2, it has also been shown that they are unable, by voluntary hyperventilation, to lower their arterial pCO_2. The diminished response to CO_2 may be related to the reduced ventilatory capacity. However, although the restriction of maximal breathing capacity obviously sets a ceiling to the ventilation that could be achieved with the inhalation of CO_2, Prime and Westlake and Alexander and associates did not feel that the lowered response to CO_2 could be explained on the basis of the mechanical ventilatory defect and attributed it to a diminished sensitivity of the respiratory center. Tenney demonstrated that the diminished responsiveness to CO_2 correlated well with the degree of CO_2 retention, changing in a manner which was inversely proportional to the degree of CO_2 retention.

However, as long ago as 1920, Scott suggested that the increased buffering power of the blood and tissue fluids explained the reduced respiratory sensitivity. It is still not clear whether his suggestion does not explain the findings which have been interpreted to indicate a change in the sensitivity of the medullary respiratory center. When the CO_2 retention is buffered by retention of bicarbonate, a compensated gaseous acidosis will result and there will be an apparent diminished response to the inhalation of CO_2, since for any given rise in CO_2 tension there will be less increase in hydrogen ion concentration than in a normal individual.

Thus the diminished ventilatory response to CO_2 in patients with severe pulmonary emphysema is probably due to several factors. These are the increased buffering, delayed intrapulmonary mixing, reduced ventilatory capacity and possibly diminished sensitivity of the medullary respiratory center.

When the respiratory system loses its ability to respond to excessive levels of CO_2 in emphysema, there is a fall of arterial O_2 tension and subsequent stimulation of the peripheral chemoreceptors. These receptors now become the principal regulators of the respiratory drive and anoxemia the primary stimulus. When the

arterial O_2 tension is raised by the administration of oxygen, the peripheral chemoreceptors are no longer stimulated and a further diminution in pulmonary ventilation takes place. As a consequence, the arterial CO_2 tension may rise to exceedingly high levels, and coma and even death may ensue.

It is apparent that many factors are responsible for the sequence of events leading to respiratory acidosis. The primary disturbance is an inadequate alveolar ventilation relative to the metabolic production of CO_2 by the body. During exercise the patient with emphysema is unable to meet the increased ventilatory demands. The development of pulmonary infection or congestion and bronchospasm will also reduce the effective alveolar ventilation as well as increasing the work of breathing and the metabolic production of CO_2, resulting in an elevation of arterial pCO_2. The administration of oxygen, barbiturates or narcotics to patients in whom the medullary respiratory center is depressed also leads to diminution in alveolar ventilation and retention of carbon dioxide.

Clinical Manifestations

Acute respiratory acidosis should be suspected in any emphysematous patient in whom acute respiratory infection such as bronchitis or bronchopneumonia, asthma or acute heart failure has developed. The clinical signs which may be elicited are those due to the primary disease process, those due to the precipitating factors, and those due to CO_2 retention itself.

Clinical examination reveals diminished movement of the chest wall, little or no movement of the diaphragm and signs of diffuse bronchial obstruction. The patient is frequently cyanosed and extremely dyspneic.

Although acute retention of CO_2 is frequently precipitated by an acute infection, constitutional signs of infection are minimal or absent, the temperature being subnormal in many cases; the white blood count is low, normal or a little elevated. Congestive heart failure, which is also frequently precipitated by the acute infection, is often present, and other cardiovascular signs such as generalized vasodilatation with profuse sweating and peripheral

collapse may be present There is frequently a marked tachycardia, and blood pressure may be high, low or normal

Chronic respiratory acidosis is not usually associated with any recent acute episodes of infection but may develop insidiously This condition should be suspected when chronic cor pulmonale and polycythemia are present, since they are frequently associated with chronic CO_2 retention

The manifestations of respiratory acidosis are frequently precipitated by the administration of oxygen to patients in whom anoxia is a prime stimulus to respiration The clinical findings are predominantly neurologic, the severity depending on the level of hypercapnia and acidemia

Disturbances of consciousness are most frequently observed The patient may be very depressed or show evidence of confusion and hypomanic activity with hallucinations Extreme lassitude, drowsiness, somnolence and coma may eventually develop The causes of these mental changes is uncertain

Muscular movements such as fine tremors of the facial muscles and intermittent jerking of the fingers and arms are a characteristic feature of CO_2 narcosis Coarse myoclonic jerking of the trunk and arms and occasionally generalized convulsions may occur The limbs are flaccid in severe states and the tendon reflexes absent The plantar responses either remain flexor or are equivocal, although Meduna has occasionally elicited an extensor plantar response in very deep CO_2 narcosis

The pathophysiology of the neurologic manifestations of respiratory acidosis have not been adequately explained Comroe Bahnson and Coates suggested that several factors might be responsible for the coma induced by oxygen administration in severe emphysema, namely CO_2 narcosis, cerebral vasospasm, direct or reflex depression of the cerebral cortex by high oxygen tension or increased cerebrospinal fluid pressure However, Patterson, Heyman and Duke have demonstrated that an elevated arterial pCO_2 is responsible for an increased cerebral blood flow Davis and MacKinnon observed that breathing oxygen caused a rise in cerebrospinal fluid pressure in cor pulmonale, and Simpson

showed that the inhalation of CO_2 did the same. It would appear that the increased cerebral blood flow associated with an elevated arterial pCO_2 may account for the headache and some of the mental changes. Papilledema may also develop although the mechanism of its development is uncertain.

Barach has stated that the deleterious effects of CO_2 retention can be avoided if the pH is kept in the normal range. Although this is true to some extent, the presence of hypercapnia, even though compensated, can bring about considerable clouding of the sensorium and severe headache. Also, although some of the clinical manifestations of respiratory acidosis may be encountered in other conditions with lowered pH, it would appear that the presence of hypercapnia in addition to acidemia greatly increases the severity of the neurologic signs and symptoms.

Laboratory Confirmation

Analysis of the arterial blood gases by the bubble technique will reveal anoxia and an elevated CO_2 tension establishing the diagnosis of CO_2 retention. Although this may be the result of either a metabolic alkalosis or a respiratory acidosis, the arterial pH will establish the correct diagnosis and the degree of acidemia.

In acute respiratory acidosis, the total CO_2 content may be little elevated, and the CO_2 combining power or the whole blood buffer base (Singer and Hastings), both indices of alkali reserve, will be normal. In chronic respiratory acidosis, on the other hand, when compensation has taken place, the CO_2 content will be high. At this stage the CO_2 combining power will be elevated, and in the presence of an acid urine, will aid in establishing the diagnosis.

Arterial pH and pCO_2 should be determined at intervals in order to evaluate therapy and the progress of the condition. The CO_2 combining power will be useful only as an index of the secondary lowering of bicarbonate as a result of the improvement of arterial pCO_2.

MANAGEMENT

The therapeutic approach to respiratory acidosis should be based on the physiologic disturbances present. It is obvious that

therapy should be primarily directed towards provision of an adequate ventilation and an increased elimination of CO_2. Thus, treatment should be designed to reduce the work of breathing by relieving the airway obstruction or pulmonary congestion. When intensive therapeutic measures fail to lower the arterial pCO_2, mechanical aids to respiration may provide an adequate alveolar ventilation.

The development of CO_2 retention can frequently be avoided by preventative measures. However when CO_2 retention occurs active therapy must be instituted.

Active Therapy

ANTIBIOTICS

Acute elevation of pCO_2 and congestive heart failure are often precipitated by an acute infection in patients with severe emphysema. The infection, with excessive secretions which may be difficult to raise and inflammatory swelling of the bronchiolar mucosa or possibly broncho-spasm, plays a major role in airway obstruction. Control of infection must therefore be achieved early and intensive antibiotic therapy, particularly penicillin, should be instituted immediately.

BRONCHODILATORS

Aerosol inhalation of Isuprel, (1-3'-4' dihydroxy-phenyl-2-isopropyl-aminoethanol hydrochloride 1:200), Vaponefrin (2.25 per cent racemic epinephrine hydrochloride) or other ephedrine-epinephrine mixtures are exceedingly helpful in reducing broncho-spasm and the mechanical work of breathing.

The work of breathing done on the lungs can be estimated by simultaneous measurement of oesophageal pressure and air flow and differentiated into work required to overcome elastic resistance and viscous resistance. Figure 14.1 demonstrates the effect of nebulized bronchodilator on elastic and viscous work of breathing in a group of 18 patients with emphysema. These results are taken from data reported by Cherniack. It can be seen that a single administration of bronchodilator resulted in a marked reduction of both elastic and viscous work of breathing.

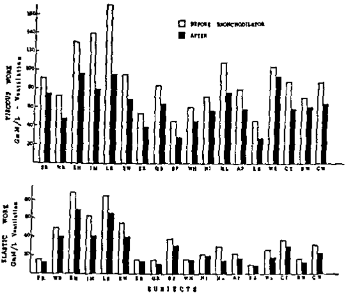

FIG. 14.1 The effect of nebulized bronchodilator on work required to overcome elastic and viscous resistance in 18 patients with emphysema.

Cohn, Carroll and Riley have published excellent results using intensive nebulized bronchodilator in acute respiratory acidosis Patients who are able to cooperate should be asked to exhale maximally before inhaling the aerosol, thus carrying the bronchodilator deep into the bronchial tree. Severely obstructed patients should be given nebulized bronchodilator for 5 minutes every 30 to 60 minutes. If the patient is unable to cooperate sufficiently to take a deep breath, the bronchodilator aerosols may be administered with an intermittent pressure breathing apparatus

Aminophylline may be administered freely by vein or rectum and is frequently exceedingly helpful in initiating treatment in patients whose airways are so severely obstructed that inhaled bronchodilator cannot reach the bronchioles in appreciable quantities The diuretic effect of aminophylline, by reducing pulmonary congestion, will also be beneficial in reducing the work of breathing.

Oral aminophylline with or without ephedrine should be administered 3 to 4 times daily, preferably on an empty stomach

TREATMENT OF HEART FAILURE

The presence of pulmonary congestion alters the elastic properties of the lung and increases the work required to overcome elastic resistance Digitalis should be administered whenever heart failure is present The patient should be placed on a salt-free diet and diuretics administered when necessary Figure 14 2 demonstrates the effect of diuretics on the arterial pCO_2 in a patient with emphysema and cor pulmonale The arterial pCO_2 remained high in this patient despite intensive bronchodilator and intermittent positive pressure breathing therapy It is probable that retention of CO_2 in this case was predominantly due to an increased elastic resistance to lung distension which was associated with pulmonary congestion

Carbonic anhydrase inhibitor "Diamox" has been reported by several workers to produce favorable results in respiratory acidosis, others have been less enthusiastic In our hands it has been

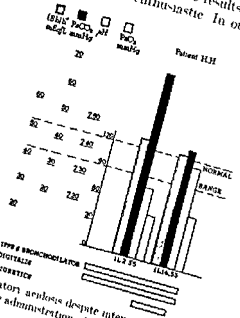

Fig 14 2 Respiratory acidosis despite intensive IPPB bronchodilator therapy and digitalis The administration of mercurial diuretics resulted in dramatic improvement

useful in patients with respiratory acidosis and pulmonary congestion in whom the administration of Diamox has resulted in a marked diuresis

OXYGEN

All patients with respiratory acidosis are suffering from a considerable degree of anoxia which must be relieved. The hazards of the administration of oxygen to patients who are unable to maintain an adequate alveolar ventilation have been emphasized by many. Barach has suggested that coma may be prevented if a low concentration of oxygen (30 per cent) is used to initiate therapy and higher concentrations are employed later. Cohn and associates and Donald have recommended that oxygen be administered intermittently, by removing the patient from the high oxygen atmosphere for at least 20 minutes out of every hour

The administration of a He-O_2 mixture which has a reduced density compared to air, will diminish the turbulent resistance in the airways of a patient with increased obstruction to air flow Thus breathing a He-O_2 mixture (80–20) will reduce the work of breathing required to overcome airway resistance.

If, during oxygen therapy, increasing mental stupor or confusion, decrease in ventilation, or elevation of arterial CO_2 tension occurs, despite concomitant bronchodilator therapy, some mechanical aid to respiration is indicated.

MECHANICAL AIDS TO RESPIRATION

Mechanical assistance to respiration is frequently required in the management of CO_2 narcosis Positive pressure breathing may be administered by either applying a positive pressure to the upper airway as with most intermittent pressure breathing units, or reducing the pressure around the body as with the Drinker type of respirator

The application of positive pressure breathing, particularly to patients with peripheral vascular collapse, may lead to further reduction in blood pressure and cardiac output This can usually be returned towards normal with negative pressure breathing during expiration which can be achieved either by applying a negative

pressure to the upper airway during expiration or a positive pressure around the body during expiration

Sarnoff and associates originally advocated electrophrenic respiration in the management of respiratory acidosis, Boutourline-Young and Whittenberger, Stone and associates, and Lovejoy and associates have demonstrated that CO_2 narcosis can be successfully treated by mechanical artificial respiration in the Drinker type of respirator However, the occasional patient may be unable to lie flat in a body respirator and in severely obstructed patients who are unable to cooperate, ventilation may actually decrease when such measures are attempted We have found the respirator to be of some value, particularly if used in conjunction with mechanical exsufflation

Mechanical exsufflation, devised by Barach and associates as a means of eliminating secretions in patients with an ineffective cough, has been shown by Chermack to be superior to the conventional respirator in managing the acid base disturbance associated with respiratory acidosis in emphysema This was presumably due to removal of bronchiolar secretions, thus allowing a more effective alveolar ventilation Examples of the beneficial effect of the exsufflator early in the management of respiratory acidosis are demonstrated in Figures 14 3 and 14 4 In patient W B (Fig 14 5) the arterial pCO_2 was exceedingly high despite oxygen, intensive bronchodilator, antibiotic and heart failure therapy A short course of exsufflation resulted in immediate lowering of arterial pCO_2 and marked clinical improvement

Recently exsufflation with negative pressure, the "cofflator," which requires more patient cooperation, has been attempted in the management of respiratory acidosis and has proved beneficial particularly where excessive secretions were present

The prime use of the respirator, exsufflator and in some instances, the cofflator is in the management of the comatose or extremely fatigued patient The exsufflator and cofflator are also of particular value if rapid hyperventilation and raising of excessive secretions are desired

In our hands intermittent positive pressure breathing units (IPPB) have proved an exceedingly useful and practical adjunct

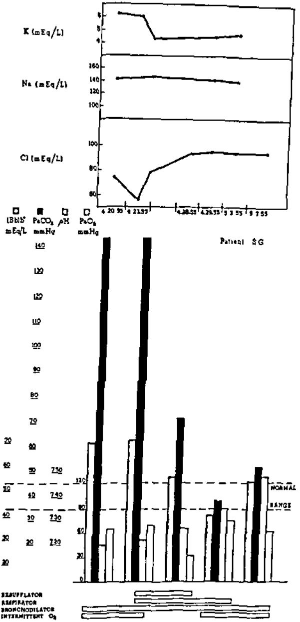

FIG 14 3 Severe respiratory acidosis with secondary elevation of whole blood buffer base Note very low chloride and elevated potassium associated with high pCO_2 Exsufflator resulted in fall of pCO_2, whole blood buffer base and potassium, and rise of chlorides.

to the management of CO_2 narcosis This method of therapy is particularly useful in the conscious individual in whom orthopnea is a great problem, and who therefore is unable to lie flat in the respirator In addition, it is much easier for the patient in the sitting position voluntarily to raise secretions Skillfully managed, the patient-operated IPPB provides a means of administering oxygen without diminution in ventilation It also provides a convenient and effective means of administering nebulized bronchodilators and detergents Since this apparatus requires that the patient produce an initial negative pressure in the thorax to initiate inspiratory negative pressure, it is immediately apparent that the patient who is extremely fatigued may be unable to activate the machine Also, constant attention is required whenever using IPPB since, while breathing oxygen, the patient may actually depress his minute ventilation considerably The patient

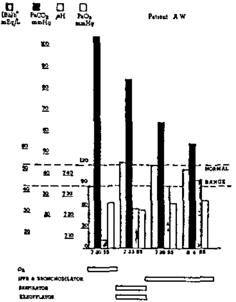

FIG 14 4 Severe respiratory acidosis precipitated by oxygen therapy Exsufflator followed by IPPB and bronchodilators resulted in marked improvement

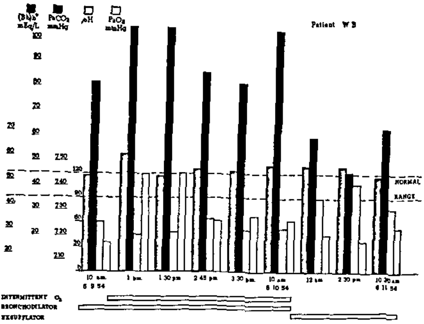

FIG 14 5 Severe respiratory acidosis which failed to improve despite intermittent oxygen and intensive bronchodilator therapy. A short course of exsufflation resulted in striking clinical improvement

must, therefore, be encouraged constantly to take deep breaths as long as IPPB is administered Examples of the beneficial effects of IPPB therapy in respiratory acidosis are demonstrated in Figures 14 4, 14 6 and 14 7 IPPB was administered to A W (Fig 14 4) after initial exsufflation, while E. H. (Fig 14 6) and A R (Fig 14 7) received IPPB therapy alone

Most of the mechanical aids usually result in better drainage of secretions and increased expectoration When mechanical aids are inadequate in raising secretions, bronchoscopic aspiration of the retained secretions should be undertaken Rarely tracheotomy may be required

ELEVATION OF THE DIAPHRAGM

Pneumoperitoneum and elastic or pneumatic belts elevate the diaphragm to a more favorable position Wright and associates and Gaensler and Carter have demonstrated improvement in

symptoms and pulmonary function following pneumoperitoneum in emphysema, Callaway and McKusick have reported favorable results using pneumoperitoneum in the therapy of respiratory acidosis Barach and Gordon have advocated the wearing of a special support to obtain abdominal compression and to elevate the diaphragm in order to improve ventilatory function and the coughing mechanism Although the rationale for these measures which restore the diaphragm to a more normal position is a reasonable one, we have not been impressed with the results we have obtained

BREATHING EXERCISES

Dramatic benefits following breathing exercises have been emphasized by Barach, Gay, Miller, and Allan When the patient is taught to breathe with his diaphragm, with the lips pursed during expiration, marked subjective improvement with increased exercise tolerance results Breathing exercises promote the effective-

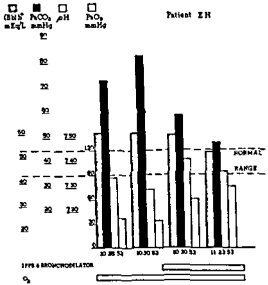

FIG 14 6 Respiratory acidosis which improved rapidly when treated by intensive IPPB and bronchodilator therapy

ness of both diaphragmatic and intercostal muscles, resulting in a more efficient ventilation, probably due to a slowed respiratory *rate and a more efficient distribution of inspired gas. The beneficial* effect of a slowed respiratory rate is illustrated in Figure 14 8 This data was obtained from patients previously reported by Cherniack. It can be seen that a slowed respiratory rate resulted in an increased compliance of the lung indicating reduced elastic resistance to respiration in 18 emphysematous patients. Since it is well established that slowed respirations also reduce viscous resistance, it is apparent that the slowed respiratory rate results in a considerable reduction in work of breathing in patients with emphysema

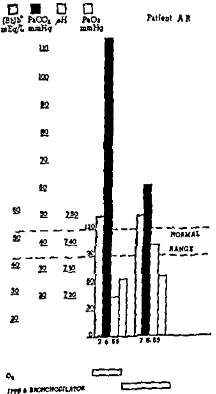

Fig 14.7 Severe respiratory acidosis with marked improvement following IPPB and bronchodilator therapy.

LIQUEFYING AGENTS

The presence of bronchiolar obstruction due to thick, viscid secretions is frequently a considerable factor in the development of anoxia and CO_2 retention in severe emphysema. The administration of potassium iodide, three times daily, nebulized liquefying enzymes or detergents such as Alevaire and adequate humidification of the inspired air aid greatly in liquefying the sticky secretions, making them easier to raise and thereby diminishing airway obstruction. However, it must be recognized that potassium iodide, if not used concurrently with intensive therapy directed at reducing the CO_2 retention, may increase the possibility of hyperkalemia.

CORTISONE AND ACTH

Numerous workers have demonstrated relief of bronchial obstruction following cortisone and ACTH. The newer steroids, prednisone and prednisolone are even more useful since they do

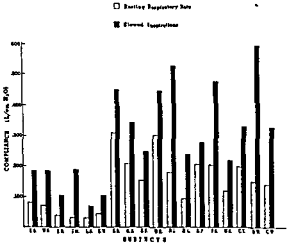

FIG. 14-8 The effect of a slow inspiration on the compliance of the lungs in 18 patients with emphysema.

Note marked increase in compliance indicating reduced elastic resistance to respiration.

not cause sodium retention. Although no data are available concerning the use of these drugs in the magagement of respiratory acidosis, their beneficial effect in status asthmaticus suggests their probable usefulness, though the possibility of masking infection must always be recognized

THERAPY DIRECTED AT THE ACIDEMIA

Barach has suggested that the deleterious effects of respiratory acidosis can be avoided by maintenance of a normal pH and has therefore suggested the use of intravenous sodium lactate to restore pH towards normal. Although such measures may alleviate some of the neurologic manifestations of respiratory acidosis, this form of therapy should only be considered palliative since the basic defect remains, and the vicious circle of hypoventilation and hypercapnia still continues

RESPIRATORY STIMULANTS

Little beneficial effect has been reported using respiratory stimulants, although Westlake and associates advocate intravenous nikethamide, intravenous caffeine sodium benzoate and amphetamine have also been suggested

Preventive Therapy

(1) These patients should be warned not to undertake excessive activity The normal respiratory response to exercise is in proportion to the increased metabolic demands of the body. In emphysema, Cournand and associates observed that the oxygen cost of breathing was markedly elevated, particularly when the ventilation was increased

(2) Each upper respiratory infection must be treated intensively since these patients tolerate even the most minor infections poorly

(3) Oral aminophylline and ephedrine preparations and nebulized bronchodilators should be used daily in order to maintain patent airways.

(4) Diaphragmatic breathing exercises should be encouraged until diaphragmatic breathing continues without conscious effort

(5) Narcotics and sedatives which tend to depress the respiratory centers should be avoided or administered with the greatest of care to patients with severe emphysema because of the likelihood that further depression of respiration will occur

(6) CO_2 inhalation should be avoided Although normally a respiratory stimulant, it may act as a narcotic in a patient with severe emphysema and further depress ventilation

Thus it can be seen that early recognition of this condition and the avoidance of precipitating causes is important in the prevention of the deleterious effects of CO_2 retention Measurement of arterial pCO_2 and pH assist in the early diagnosis Management of the condition when it develops should be directed at reducing the work of breathing and provision of an adequate alveolar ventilation Estimation of arterial blood gases at intervals will aid greatly in assessing therapy and the progress of the condition

Summary

Respiratory acidosis or retention of CO_2 is not infrequently encountered in patients with severe emphysema, often being precipitated by infection, increased work of breathing, or the administration of oxygen The elevated arterial pCO_2 is the result of a reduced alveolar ventilation

Although this condition has usually been considered to have a fatal termination, the application of therapy directed at improving the physiologic disturbances which are present has resulted in complete reversal of the condition in many instances Therapy should therefore, be directed towards elimination of CO_2 by reduction of airway obstruction and pulmonary congestion and/or by the use of mechanical respirators to insure an adequate alveolar ventilation

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Chapter 15

COR PULMONALE IN CHRONIC PULMONARY EMPHYSEMA

DICKINSON W RICHARDS, M D, AND ALFRED P FISHMAN, M D

INTRODUCTION

Cor pulmonale may be defined as a heart which has a significant degree of dilatation, hypertrophy or failure, secondary to disease of the lungs In our experience, the manifestations of heart strain are confined to the right side of the heart, the physiologic disturbances incident to the pulmonary disease, such as hypoxia or altered pulmonary mechanics, or augmented bronchial artery flow, apparently do not cause left ventricular hypertrophy or failure Consequently, if the left ventricle manifests strain or disease in a patient with lung disease, it is to be ascribed to separate and intrinsic hypertensive, coronary artery, valvular, or myocardial disease

This definition of cor pulmonale implicity excludes right heart involvement secondary to rheumatic valvular heart disease

It is worthy of emphasis that the great majority of patients with mild to moderate chronic pulmonary emphysema do not develop cor pulmonale, the latter being a late complication of severe forms of the disease The particular types of emphysema in which cor pulmonale is likely to occur, and the manner of its development in each, are considered later in this section

PHYSIOLOGIC CONSIDERATIONS THE CIRCULATION IN CHRONIC PULMONARY EMPHYSEMA

The circulatory changes which may develop in chronic pulmonary emphysema stem from three distinct, but interrelated

anatomic alterations (1) A decrease in pulmonary parenchymal *elasticity* caused by the chronic inflammatory, atrophic, or fibrotic processes (2) A restriction of the pulmonary vascular bed caused by a combined decrease in *distensibility* and in *cross-sectional area* of the pulmonary blood vessels, these alterations in distensibility and capacity stem from pathologic changes in the perivascular supporting structures, as well as in the vessels proper (3) *Obstruction* to air flow by stenoses and exudates along the ramifications of the tracheobronchial tree This airway obstruction acts, in conjunction with the distortion, thickening and partial obliteration of segments of the alveolar-capillary interface, to disrupt the normal balance between distribution of inspired gas and perfusion of the pulmonary capillaries

It seems worthwhile at this point to distinguish, on the basis of these anatomic changes, the particular patient with chronic emphysema who may be expected to develop pulmonary hypertension and cor pulmonale. Obviously, the subject with nonobstructive emphysema who has lost pulmonary elasticity due to atrophic changes may manifest augmented repiratory effort; although the increased respiratory excursions will, *per se*, affect the flow of blood through the lungs, they are not of considerable hemodynamic significance Similarly, the mere restriction of segments of the capacious pulmonary vascular bed by inflammation and scarring in a patient ... is generally inadequate to elicit th ... requisite for the evol ... hand, it is the combination of. (a) diffuse, rather than segmental pulmonary involvement, causing ventilatory insufficiency, and (b) disturbances in gas exchange—hypoxia and hypercapnea—which is generally responsible for the evolution of chronic cor pulmonale Although secondary development of pulmonary arteriosclerosis is sometimes a significant added factor, often it is not

Before considering in greater detail the effect of the interplay of these factors on the evolution of pulmonary hypertension and cor pulmonale, it would seem advisable to review the isolated effect of each one, *per se*, on the circulation

The Effects of Decreased Pulmonary Elasticity

In patients with chronic obstructive pulmonary emphysema, the mechanical effect of respiration is exerted primarily on the pulmonary, rather than on the systemic circulation for two reasons (1) The pulmonary circulation is directly exposed to the mechanical effects of the stresses and strains of respiration via the intrathoracic pressure changes (2) There is no equivalent in the pulmonary circulation of the baro-regulative system which minimizes fluctuations in blood pressure in the systemic circulation However, lesser degrees of change in blood pressure due to respiration are detectable in the systemic circulation

Hemodynamic effects of the respiration on the circulation in intact man have been inferred solely from an analysis of pressure pulses recorded from various cardiac chambers and the major arteries, this limitation is due to the lack of any independent method for quantitatively estimating cyclic changes in blood flow in the brief periods under consideration However, from an analysis of the pressure pulses in man, and by inference from animal experiments, it is generally accepted that in normal subjects, respiration affects the circulation primarily by effecting the displacement of increments of blood into and out of the thoracic vessels Considerable aid in effecting pressure gradients favorable for flow is contributed by the cyclic changes in intrathoracic pressure which characterize the respiratory cycle In this light, a review of the effects of respiration on the circulation in normal human subjects seems in order since the respiratory influence in emphysema is qualitatively comparable to the patterns observed in normal subjects during augmented breathing The changes in the circulation imposed by one respiratory cycle are schematically illustrated in Figure 15 1

During inspiration, the intrathoracic pressure decreases more than right atrial or right ventricular diastolic pressure, the filling pressure of the right heart is thus increased This augmented filling pressure is a reflection of the increased volume flow to the right heart Although the increased distending volume in the right

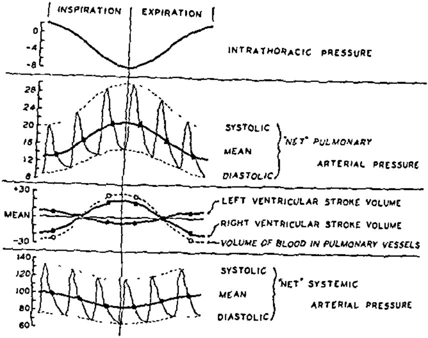

Fig 15 1. Schematic representation of the influence of respiration on the circulation during one respiratory cycle of moderate depth All pressures are expressed in mm Hg Discussed in text (From Lauson, Bloomfield and Cournand Am J Med, 1: 315, 1946)

ventricle leads to an augmented output from the right heart, the effect of this augmented output on pulmonary artery pressure represents a balance between two opposing factors: (1) The increased stroke volume ejected into the pulmonary circulation (2) The passively induced increase in capacity of the pulmonary vascular bed

The retention of blood in the pulmonary circulation is reflected by the progressive increase in pulse pressure in the pulmonary artery and right ventricle during inspiration and the concomitant decrease in pressure in the systemic circulation

During expiration, intrathoracic pressures increase more than right atrial and right ventricular diastolic pressures; the net filling of the right heart is thereby diminished The pattern described above for inspiration is consequently reversed Indeed, from the

point of view of the circulation, the lung has been likened to a sponge, imbibing and withholding blood from the systemic circulation during inspiration, and expressing blood into the systemic circulation during expiration

In some patients in whom expiration becomes an active process, an actual obstruction to venous return may obtain as positive intrathoracic pressures are imposed on central venous pressures It is, however, of interest that the venous valves distal to the thorax normally prevent the retrograde transmission of the rise in central venous pressure during expiration until valve competency is lost, as in central venous congestion Therefore, in normal subjects and in patients with chronic pulmonary emphysema, the rise in peripheral venous pressure during expiration reflects merely gradual filling of a distensible system which is obstructed at its thoracic outlet

The observations on the changes in pulse pressure during the respiratory cycle have led to the conclusion that the behavior of the right and left heart during respiration is, at least in a general fashion, in accord with Starling's law The reverse effects on cardiac performance, induced by artificial respiration with positive pressure breathing apparatus, have also been interpreted in this light Thus, inspiration produced by the inflow of air under positive pressure, by impeding venous return, results in a decrease in net filling pressure in the right heart with lowered right ventricular and pulmonary artery pressures, the systemic arterial blood pressures simultaneously increase, suggesting an increase in left ventricular output During passive expiration, right heart net filling pressure and right ventricular and pulmonary artery pulse pressures increase whereas systemic arterial pulse pressures decrease The sequential changes outlined above are schematically represented in Figure 15 2 The therapeutic implications of this type of physiologic observation have been taken into account in the design of positive pressure respiratory equipment, since, in order to maintain the circulation, positive pressure inspiration cannot be unduly prolonged, and expiration must be of adequate duration and either unopposed or facilitated

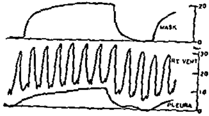

FIG. 15 2. Schematic representation of the influence of pressure breathing on right ventricle filling and pulse pressures. Tracings from above downward include: (1) mask pressure, inspiration and expiration; (2) right ventricular pressure, (3) intrapleural pressure

During inspiration, as mask pressure and pleural pressure increase, filling pressure at the right heart progressively diminishes; this is manifested by a decrease in the difference between intrapleural and diastolic pressures in the right ventricle Pulse pressure in the right ventricle is also reduced, suggesting decreased stroke volume During expiration, the reverse occurs The ability of expiration to compensate for the inspiratory deficit in blood flow is facilitated by the prompt return of expiratory mask pressure curve to ambient pressure. (From Richards, Cournand and Motley Trans Am Phys, 59: 102, 1946)

Pulmonary Hypertension and Cor Pulmonale

The respiratory swings in pulse pressure, described above for normal subjects, occur in an exaggerated fashion in virtually all patients with chronic obstructive pulmonary emphysema. As illustrated in Figure 15 3, they are manifest at rest while breathing ambient air and become more marked as respiration is further stimulated Nonetheless, they apparently contribute little to the genesis of chronic cor pulmonale Of greater import from this point of view are. (1) The restriction and altered distensibility of the pulmonary vascular bed (2) The arterial hypoxemia induced by impaired gas exhange. (3) The degree of polycythemia and hypervolemia congesting b... systemic and ... y vascular systems However, bef... further t... these factors in the developmen... ...nale, ...cessary to establish a working ... pulmon...

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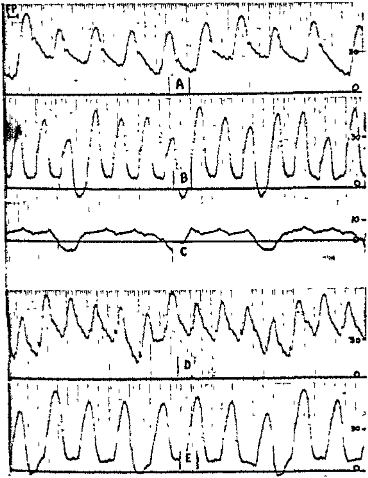

Fig. 15 3 Right heart pressures in a patient with emphysema and cor pulmonale, at rest and during augmented ventilation

A–C Pressure pulses recorded from the pulmonary artery right ventricle and right atrium during quiet breathing There is pulmonary hypertension at rest (A), with normal end-diastolic pressures in the right ventricle (B) and normal right atrial pressure (C) indicating the absence of right heart failure Even at rest, the effect of breathing upon the pressure pulses is greater than normal

D–E Pressure pulses recorded from the pulmonary artery and right ventricle during 5 per cent CO_2 breathing Note the exaggerated influence of respiration on the circulation

In this patient, there was an increment in pulmonary artery pressure during CO_2 breathing which was associated with a concomitant increment in pulmonary blood flow Discussed in text (From unpublished data by Fishman Fritts and Cournand)

mented pressure-work of the right ventricle is frequently supplemented by an augmented volume-work due to increased cardiac output. Both lead to right ventricular hypertrophy and dilatation.

Clinically, the diagnosis is established by the demonstration of right heart enlargement, with or without failure, in a patient with primary pulmonary disease. Unfortunately, in these patients, the clinical diagnosis of either pulmonary hypertension or right heart strain prior to definite enlargement or failure is not readily established. For example, although an accentuated pulmonic second sound frequently occurs in these patients with pulmonary hypertension, the association is not invariable. Furthermore, electrocardiographic evidence of right heart strain occurs regularly only when pulmonary artery mean pressure is twice normal, and clear-cut roentgenologic evidence of right heart strain becomes available only after pulmonary hypertension is marked and there is a considerable degree of right heart enlargement. Consequently, the clinical diagnosis of pulmonary hypertension and cor pulmonale without heart failure is often a retrospective one, made after the onset of obvious right heart failure in a patient with known pulmonary disease. Considerable insight into the development of chronic cor pulmonale has been provided with the advent of right heart catheterization. The use of this technique has led to the detection of pulmonary hypertension and the establishment of the diagnosis of cor pulmonale prior to, as well as after, the onset of right heart failure.

The Effects of Decreased Pulmonary Vascular Distensibility

In the normal human subject, the pulmonary vascular bed constitutes a voluminous, highly distensible system which is capable of accommodating the same flow as the systemic circulation at approximately 1/10th the perfusion pressure. Thus, with total cardiac output normally ranging from 2.6 to 3.5 l./min./sq. m of body surface, pulmonary artery pressures generally do not exceed a systolic pressure of 25 mm. Hg and a diastolic pressure of 10 mm. Hg. Indeed, a pulmonary artery pressure in excess of 30 mm. Hg or a mean blood pressure in excess of 15 mm. Hg, con-

stitutes unequivocal pulmonary hypertension These low pressures, in the face of identical blood flows, indicate that the work done by the right ventricle is normally less than the left; this is reflected in the unequal myocardial masses The high-distensibility involves all segments of the pulmonary vascular tree, and stems (a) from the anatomic composition of the small pulmonary arteries which are strikingly deficient in smooth muscle, (b) from the lack of well-defined sphincteric arterioles, and (c) from the paucity of perivascular supporting tissue, so that tissue pressure opposing vascular distension is negligible

In patients with chronic pulmonary emphysema, the cross-sectional area and distensiblity of the pulmonary vascular bed are reduced and the intravascular resistance to blood flow is thereby increased Several interrelated pathologic mechanisms are involved (1) Thinning-out and obliteration of pulmonary capillaries due to hyperinflation of alveoli, and atrophic degeneration of alveolar walls, this occurs in both the atrophic and obstructive forms of emphysema (2) Thickening of the walls of the small muscular vessels accompanied by obliteration of segments of the vascular bed by inflammation and fibrosis, the role of this factor is determined by the presence of chronic bronchial and parenchymal infection (3) Increase in tissue pressure surrounding the blood vessels through the same perivascular infiltrations and fibrosis (4) Loss of distensibility through increased pulmonary blood volume (5) Pulmonary arteriosclerosis (6) Possible (but not proven) pulmonary vasomotor effects

The contribution of this diminished distensibility to the evolution of pulmonary hypertension may be inferred from observations on normal human subjects as well as from patients with restricted vascular beds Thus, in normal human subjects, an increase in blood flow to three times normal can be accommodated with only a minimal (2 to 3 mm Hg) increase in pulmonary artery pressure This high degree of distensibility is further exemplified by patients with only one normal lung following pneumonectomy, in whom a threefold augmentation in blood flow fails to increase pulmonary artery pressure to abnormal levels, how-

ever, even in the normal lung, and particularly in the presence of restricted vascular beds, further augmentation of flow may elicit pulmonary hypertension

Further insight as to the role of increased blood flow in causing pulmonary hypertension has been provided by observations on the effects of acute digitalization in patients with chronic pulmonary emphysema and cor pulmonale in frank congestive heart failure In these subjects, the augmentation of pulmonary blood flow elicited by the intravenous administration of Digoxin is associated with an increase in pulmonary artery systolic and pulse pressure, which are responses characteristic of an increased flow into a more rigid vascular bed This response is illustrated in Figure 15 4

These pulmonary blood flow and pressure relations for vascular beds of different distensibilities, have been synthesized into a schematic representation as illustrated in Figure 15 5 In this figure, blood flow through the lungs is schematically represented along the abscissa in multiples of normal pulmonary blood flow; the ordinate represents pulmonary artery mean pressure in arbitrary multiples of normal mean pulmonary artery blood pressure. It is clear from this oversimplified diagram, that the normal pulmonary circulation is capable of accommodating large increments in blood flow with little increase in pressure; on the other hand, in the vascular bed restricted by chronic pulmonary emphysema, the entire pressure-flow curve is shifted to the left, resulting in an abnormally large increment in pressure for each increment in blood flow

It should be emphasized again that the great majority of patients with emphysema of mild to moderate degree do not develop clinical cor pulmonale In the earlier stages there is not even significant pulmonary arterial hypertension Furthermore the tendency to this complication is not necessarily correlated with loss of ventilatory function Many patients with marked ventilatory insufficiency and even some degree of arterial hypoxemia continue to the end without heart failure; in others cor pulmonale may develop terminally In brief, the natural history of chronic obstructive pulmonary emphysema may be represented as a race between

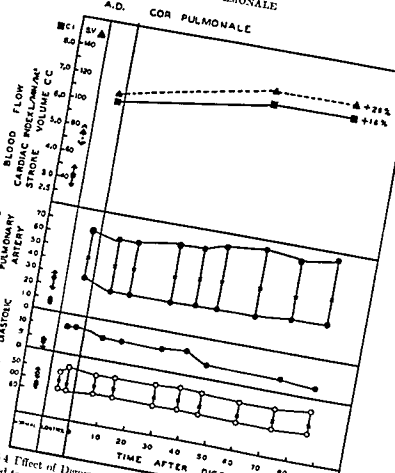

Fig 15.4 Effect of Digoxin in right heart failure due to chronic cor pulmonale Closed triangles = stroke volume, closed squares = cardiac output, closed circles = pulmonary artery systolic and diastolic and right ventricular end diastolic pressures open circles = brachial artery systolic and diastolic pressures, cross marks = mean pressures

The normal mean values and approximate range of variation are plotted in the first vertical column Note that (a) the initially elevated cardiac output rose considerably after Digoxin (b) the elevated right ventricular end diastolic pressure returned to normal and (c) with the increase in stroke volume the pulmonary artery systolic pressure rose (From Ferrer et al Circulation 1: 161, 1950)

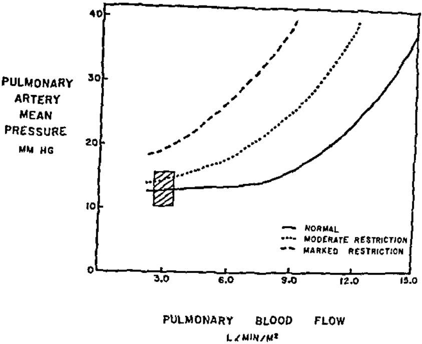

FIG 15 5 Schematic pulmonary artery pressure-flow curves in normal subjects and in patients with restricted vascular beds

ventilatory and cardiac failure, sometimes terminating as a combination of both

The Effects of Impaired Gas Exchange

It is well established that chronic obstructive pulmonary emphysema is invariably associated with an aberration in the normal relation between the distribution of mixed venous blood and the distribution of inhaled air to the alveoli This impairment in homogeneity of alveolar-ventilation and perfusion is aggravated by actual obliteration of some segments of the alveolar-capillary interface, thereby reducing the area available for gas exchange. The net effect of these pathologic alterations is an impediment to the exchange of oxygen and carbon dioxide between the ambient air and the blood perfusing the pulmonary capillaries.

Although the steepness of the CO_2 dissociation curve facilitates

the compensatory output of CO_2 from the lungs despite the disturbance in alveolar ventilation-perfusion relationships, the flat upper part of the oxyhemoglobin dissociation curve excludes a corresponding compensation for oxygen Consequently, arterial blood hypoxemia antedates CO_2 retention, and whereas in early cor pulmonale due to chronic obstructive emphysema, arterial hypoxemia, pulmonary hypertension, right heart strain may evolve gradually and subtly, in the flagrant full-blown syndrome of cor pulmonale in heart failure, CO_2 retention is also characteristically present

Two factors are operative in this cumulative rise in total CO_2 content and partial pressure (1) Failure of alveolar aeration leads to impaired elimination of CO_2 from the body, chronic elevation of P_{CO_2}* in turn, leads to a depression of the respiratory response to the P_{CO_2} stimulus, with further inadequacy of ventilation and rise in CO_2 (2) Elevated P_{CO_2} promotes the reabsorption of bicarbonate by the kidney, thereby providing another mechanism for augmenting the body CO_2 stores

This entire mechanism is greatly aggravated when the patient with CO_2 retention breathes pure oxygen, since the abolition of the anoxic stimulus to breathing decreases minute and alveolar ventilation, greatly enhancing further CO_2 retention

To what extent this retention of bicarbonate contributes to sodium and water retention, formation of edema, and aggravation of the congestive state, is not known

THE ROLE OF CHRONIC HYPOXEMIA IN ELICITING PULMONARY HYPERTENSION

Normal subjects rendered hypoxemic by prolonged stay at altitude have pulmonary artery pressures which are higher than in normal subjects at sea level In recent years, the association of arterial hypoxemia and chronic pulmonary hypertension have been repeatedly documented Indeed, in patients with chronic pulmonary emphysema, there is a direct relation between the degree of hypoxemia and the level of pulmonary hypertension

There are three general mechanisms by which chronic hypox-

* P_{CO_2} = partial pressure of CO_2 in arterial blood

emia may contribute to the onset and perpetuation of pulmonary hypertension. (1) Increased cardiac output. (2) Hypervolemia and polycythemia (3) Increased pulmonary vascular resistance to blood flow

CARDIAC OUTPUT. In the patients with chronic hypoxemia due to chronic obstructive pulmonary emphysema, cardiac output is either normal or increased In this group, despite the advent of right heart failure, cardiac output may remain high It is, however, noteworthy that there are types of obstructive pulmonary emphysema and hypoxemia, particularly those associated with considerable fibrosis, as in silicosis, in which the cardiac output may be normal or low throughout the entire history of the disease

The state of increased cardiac output, polycythemia and increased total blood volume, in conjunction with the clinical manifestations of systemic venous engorgement comprises the syndrome of "high output failure"

HYPERVOLEMIA AND POLYCYTHEMIA. It is well established that chronic hypoxemia resulting from prolonged residence at altitude is associated with an increase in total circulating blood volume, particularly in the red cell mass Similar observations have been made on patients with chronic cor pulmonale due to chronic pulmonary emphysema, by a variety of methods using plasma volume indicators alone, and simultaneous indicators for plasma and red blood cells During heart failure, both plasma volume and red cell mass increase, and both recede following treatment It is probable that the lungs participate in the partition of this augmented volume, suggesting a greater baseline distension of the pulmonary blood vessels, upon which is superimposed the cyclic pressure pulse resulting from each right ventricular ejection The greater initial volume in a system with reduced distensibility would result in a greater increment in pressure per unit of blood added to the pulmonary circulation than would obtain in a normal, more capacious and distensible system

It would also seem that the augmented circulating blood volume, by increasing the ventricular distension prior to systole, may help effect, and maintain, an augmented cardiac output

INCREASED PULMONARY VASCULAR RESISTANCE TO BLOOD FLOW There are at least two possible physiologic mechanisms which may be involved in these patients (1) Increased internal resistance to flow caused by the increased viscosity of the polycythemic blood, this is at least partly negated by the concomitant passive distension of vessels arising from the augmented pulmonary blood volume (2) Active diminution in the caliber of the smaller pulmonary vessels in response to the hypoxic stimulus

Of these two factors, the latter is probably the more important Unfortunately, the experimental counterpart of the clinical state of hypoxia, *i.e.*, chronic hypoxia with superimposed bouts of acute hypoxia, is difficult to achieve However, some insight as to the possible role of chronic hypoxemia in effecting increased resistance to flow may be gained from a brief review of the extensive experimental observations on the effects of *acute* hypoxia on the pulmonary circulation, in both normal subjects and in patients with chronic pulmonary emphysema

THE ROLE OF ACUTE HYPOXEMIA IN ELICITING PULMONARY HYPERTENSION

In patients with chronic pulmonary emphysema as in normal subjects, exposure to acute hypoxia of sufficient degree elicits an increase in pulmonary artery pressure This response is illustrated in Figure 15 6 This increment in pulmonary artery pressure is generally associated with a measurable increment in pulmonary blood flow However, in the same patients, a comparable increment in blood flow induced by exercise fails to elicit the same degree of hypertension This type of observation has led to the suggestion that some other factor in addition to an increased pulmonary blood flow is involved in the pulmonary pressor response to acute hypoxia It has not been possible in intact man to adduce evidence to support observations in animal preparations which indicate that a direct differential vasoconstrictor response of segments of the pulmonary vascular tree to the hypoxic stimulus is involved, nor has it been possible to demonstrate an active response of the sympathetic nervous system to the hypoxic stimulus. Whether there is an increase in pulmonary blood volume dur-

emia may contribute to the onset and perpetuation of pulmonary hypertension. (1) Increased cardiac output. (2) Hypervolemia and polycythemia. (3) Increased pulmonary vascular resistance to blood flow.

CARDIAC OUTPUT. In the *patients with chronic hypoxemia* due to chronic obstructive pulmonary emphysema, cardiac output is either normal or increased. In this group, despite the advent of right heart failure, cardiac output may remain high. It is, however, noteworthy that there are types of obstructive pulmonary emphysema and hypoxemia, particularly those associated with considerable fibrosis, as in silicosis, in which the cardiac output may be normal or low throughout the entire history of the disease.

The state of increased cardiac output, polycythemia and increased total blood volume, in conjunction with the clinical manifestations of systemic venous engorgement comprises the syndrome of "high output failure"

HYPERVOLEMIA AND POLYCYTHEMIA It is well established that chronic hypoxemia resulting from prolonged residence at altitude is associated with an increase in total circulating blood volume, particularly in the red cell mass Similar observations have been made on patients with chronic cor pulmonale due to chronic pulmonary emphysema, by a variety of methods using plasma volume indicators alone, and simultaneous indicators for plasma *and red* blood cells During heart failure, both plasma volume and red cell mass increase, and both recede following treatment. It is probable that the lungs participate in the partition of this augmented volume, suggesting a greater baseline distension of the pulmonary blood vessels, upon which is superimposed the cyclic pressure pulse resulting from each right ventricular ejection The greater initial volume in a system with reduced distensibility, would result in a greater increment in pressure per unit of blood added to the pulmonary circulation than would obtain in a normal, more capacious and distensible system

It would also seem that the augmented circulating blood volume, by increasing the ventricular distension prior to systole, may help effect, and maintain, an augmented cardiac output

INCREASED PULMONARY VASCULAR RESISTANCE TO BLOOD FLOW. There are at least two possible physiologic mechanisms which may be involved in these patients (1) Increased internal resistance to flow caused by the increased viscosity of the polycythemic blood, this is at least partly negated by the concomitant passive distension of vessels arising from the augmented pulmonary blood volume (2) Active diminution in the caliber of the smaller pulmonary vessels in response to the hypoxic stimulus

Of these two factors, the latter is probably the more important Unfortunately, the experimental counterpart of the clinical state of hypoxia, *i.e*, chronic hypoxia with superimposed bouts of acute hypoxia, is difficult to achieve However, some insight as to the possible role of chronic hypoxemia in effecting increased resistance to flow may be gained from a brief review of the extensive experimental observations on the effects of *acute* hypoxia on the pulmonary circulation, in both normal subjects and in patients with chronic pulmonary emphysema

THE ROLE OF ACUTE HYPOXEMIA IN ELICITING PULMONARY HYPERTENSION

In patients with chronic pulmonary emphysema as in normal subjects, exposure to acute hypoxia of sufficient degree elicits an increase in pulmonary artery pressure This response is illustrated in Figure 15 6 This increment in pulmonary artery pressure is generally associated with a measurable increment in pulmonary blood flow However, in the same patients, a comparable increment in blood flow induced by exercise fails to elicit the same degree of hypertension This type of observation has led to the suggestion that some other factor in addition to an increased pulmonary blood flow is involved in the pulmonary pressor response to acute hypoxia It has not been possible in intact man to adduce evidence to support observations in animal preparations which indicate that a direct differential vasoconstrictor response of segments of the pulmonary vascular tree to the hypoxic stimulus is involved, nor has it been possible to demonstrate an active response of the sympathetic nervous system to the hypoxic stimulus Whether there is an increase in pulmonary blood volume dur-

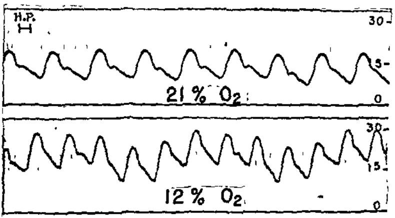

FIG 15.6 The effect of acute hypoxia on the pulmonary circulation in a normal human subject While breathing ambient air (21 per cent O_2), pulmonary artery pressure was 17 mm Hg systolic and 8 mm Hg diastolic. After 15 minutes of breathing 12 per cent oxygen, these pressures had risen to an average of 26 and 17 mm Hg respectively Note the respiratory fluctuations caused by the increased minute ventilation (From unpublished data by Fishman, Himmelstein, Fritts and Cournand)

ing acute hypoxia and its role in mechanically contributing to the pressor response is not yet established. Finally, there is no evidence, in either animal or man, to suggest that the pulmonary hypertension during moderate hypoxia may be due to back pressure from the left side of the heart

It seems valid to conclude, on the basis of available evidence, that in man, acute hypoxia of sufficient degree will consistently elicit pulmonary hypertension, the rise in pulmonary artery pressure is, in part, due to the increase in pulmonary blood flow However, the increase in blood flow is insufficient to account for the total pressor response, suggesting that either other mechanical factors, such as an increase in pulmonary blood volume, or vasoconstriction may be involved Present evidence further suggests that if vasoconstriction occurs, it is not due to the direct action of hypoxemia upon pulmonary vascular segments Finally, although some data have been gained in intact man to suggest that the autonomic nervous system is not directly involved, the role of humoral mediators have not been examined.

THE ROLE OF HYPERCARBIA IN ELICITING PULMONARY HYPERTENSION

A positive correlation exists in patients with chronic obstructive pulmonary emphysema, between high arterial blood CO_2 tensions and pulmonary hypertension This has led to considerable speculation concerning the role of the increased partial pressure of CO_2 in effecting the pulmonary hypertension Although there are no measurements available of the pulmonary artery pressures in normal subjects chronically exposed, as in submarines, to ambient CO_2, such measurements have been made during acute exposure of normal subjects, and patients with chronic pulmonary emphysema, to increased partial pressures of CO_2 in inspired air Normal subjects who breathe 5 per cent CO_2 in air for brief periods manifest no increase in pulmonary artery pressure or blood flow The effect of breathing CO_2 on right heart and pulmonary artery pressures is illustrated in Figure 15 7 In patients with chronic pulmonary emphysema, three types of pulmonary blood flow-pressure relationships have been observed during CO_2 breathing (1) No increase in flow or pressure, (2) an increase in flow without an increase in pulmonary artery pressure, and (3) an increase in blood flow *and* an increase in pulmonary artery pressure This latter response is also illustrated in Figure 15 3, D and E Although the mechanism for increased pulmonary blood flow in some patients is not clear, a likely possibility is the increase in the work of breathing due to the augmented ventilation due to breathing CO_2 At any rate, in the few patients with chronic pulmonary emphysema who do develop pulmonary hypertension while breathing CO_2, the increment in pressure seems to be fully accounted for by the increase in blood flow into a severely restricted pulmonary vascular bed As in the case of acute hypoxemia, there is no evidence to implicate vasoconstriction as a factor in effecting pulmonary hypertension

It is apparent that these limited observations on the effects of *acute* hypercarbia can only be extrapolated with reserve to the effects of *chronic* CO_2 retention upon the heart and pulmonary circulation

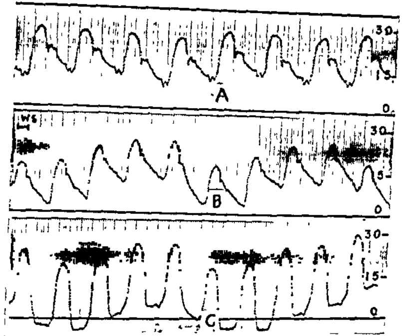

FIG 15 7 The effect of acute hypercarbia upon the pulmonary circulation in a normal human subject (A) Pulm
monary artery and righ
In the normal subject,
artery pressure (From

The Physiologic Interplay in the Evolution of Chronic Cor Pulmonale

These isolated factors may now be incorporated into a unified working concept of the evolution of pulmonary hypertension and chronic cor pulmonale as illustrated in Figure 15 8. The prime initiating factors are the restricted distensibility and anatomic distribution of the pulmonary vascular bed on the one hand and the arterial hypoxemia and chronic CO_2 retention due to impaired gas exchange on the other The arterial hypoxemia initiates a series of interplaying mechanisms, including increased cardiac output and polycythemia, recent evidence suggests that it may also be one factor in the genesis of pulmonary hypervolemia The increased pulmonary blood flow and volume, in a pulmonary

vascular bed restricted by disease, promotes the development of pulmonary hypertension The combination of pulmonary hypertension and increased cardiac output increases the pressure and the volume work of the right heart, this augmented work of the right heart leads to right ventricular hypertrophy

This schema is of course an oversimplification For example, common denominators in congestive heart failure such as salt and water retention, plethora, etc have been omitted However, his type of schema may serve to clarify the more important elationships involved in the evolution of "high output failure" some patients with chronic obstructive pulmonary emphysema Either in response to an acute episode of hypoxia precipitated bronchiolar obstruction or infection, or as the result of the gression of these inter-related mechanisms, right heart failure

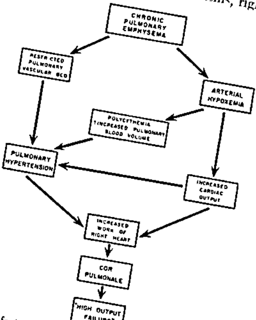

FIG 15 8 Some factors in the evolution of "high output failure" in chronic tructive pulmonary emphysema

may ensue. This right ventricular failure is characterized by a decreased stroke output from the right heart, an increase in the diastolic residual volume and in the end-diastolic pressure in the right ventricle, an elevation of mean right atrial and systemic venous pressure, and frequently, but not always, an increase in cardiac output, of particular interest in this schema, is the predominant role of hypoxia, a potentially reversible process, as an initiating and perpetuating mechanism for the increase in right ventricular work

Pulmonary artery pressures, in cor pulmonale in failure, are usually in the range 70/40 to 110/60

Retention of CO_2 and bicarbonate may be a further factor in the development or aggravation of the congestive state, their roles have not been defined.

Blood Flow Through Various Organs in Chronic Pulmonary Emphysema

KIDNEY

In patients with chronic pulmonary emphysema and cor pulmonale, renal blood flow is generally normal or increased: with the advent of heart failure, the renal blood flow is decreased It is of interest that aggravation of hypoxemia increases the renal blood flow, this is the converse of what would be expected if appreciable amounts of epinephrine were released into the circulation during acute hypoxemia Relief of hypoxemia by breathing oxygen decreases renal blood flow During relief or aggravation of hypoxemia, sodium excretion parallels renal blood flow. This sequence would suggest that in these chronically hypoxemic patients, aggravation of hypoxemia does not stimulate renal retention of sodium On the other hand, the results of these experiments have to be reconciled with the clinical observation that a more prolonged administration of oxygen to patients with this and other types of congestive heart failure has often indicated a tendency, apparent only after several days, to diuresis and loss of edema. The mechanisms underlying this latter response are complex and unresolved The effect of augmented CO_2 tensions

on promoting the reabsorption of bicarbonate and bicarbonate-bound base has been referred to above

BRAIN

Cerebral blood flow may be within normal limits in patients with chronic pulmonary emphysema but generally increases in patients with chronic cor pulmonale and heart failure In general, the cerebral blood flow is best correlated with the carbon dioxide tension in arterial blood, and less well-correlated with the corresponding oxygen tension

OTHER ORGANS

No comparable direct measurements of blood flow are available for other organs in patients with chronic pulmonary emphysema It is of interest that in normal subjects splanchnic blood volume does not decrease during acute hypoxemia

Clinical Forms of Cor Pulmonale in Pulmonary Emphysema

Although there are many minor variations in the development of cor pulmonale, three major forms can be distinguished

Acute Cor Pulmonale

This condition, arising in a patient with no previous evidence of right heart strain or failure, is not often encountered in the emphysematous subject It might be seen with such complications as multiple pulmonary embolization, or massive intercurrent pneumonia Tension pneumothorax, occasionally a complication of emphysema, may cause increased intrathoracic pressure, with backing up of the circulation, but not a critical rise in pulmonary arterial pressure or right heart failure

Acute Right Heart Failure in Chronic Cor Pulmonale

This particular state is of clinical importance due to its frequent occurrence in patients with chronic obstructive pulmonary emphysema who, prior to these attacks, manifest only mild to mod-

erate pulmonary hypertension and right ventricular hypertrophy The clinical course of these patients is characterized by a fairly stable degree of diminished ventilatory capacity which is punctuated by bouts of acute right heart failure following the imposition of a sudden stress such as undue exertion, acute bronchitis, or bronchopneumonia The stable course in the absence of stress, coupled with the rapid precipitation into circulatory crisis when a stress is imposed, identifies this group as one with a limited alveolar-capillary reserve due to a critically diminished, effective pulmonary mass This delicate balance is observed not only in patients with chronic obstructive pulmonary emphysema of advanced degree, but also in patients with a lesser degree of obstructive emphysema in whom there is the added pulmonary complication of silicosis or other diffuse fibrosis. A similar situation may also occur in the bullous, atrophic, nonobstructive type of emphysema with small amounts of effective pulmonary tissue, in marked kyphoscoliosis, and in old pulmonary tuberculosis with extensive scarring, especially following lung surgery or thoracoplasty

The common denominator in all of these states appears to be the critical restriction of the effective gas-exchanging pulmonary surface Consequently, the acute failure of the right heart is consistently associated with hypoxemia, frequently, though not always, accompanied by CO_2 retention. Polycythemia may be present but is usually far less marked than in patients with chronic progressive cor pulmonale, the latter is discussed in the next section

Symptoms of right heart failure are apt to develop gradually over a period of several days and the specific precipitating agent may be difficult to identify Thus, a bronchopneumonia sufficient to precipitate the circulatory crisis may be manifest only by a slight cyanosis, by a slight increase in cough, by a slight fever, and by a few rales and a small pulmonary parenchymal shadow on x-ray In untreated patients, a slight swelling of the ankles and enlargement of the liver may progress to a frank congestive state; hydrothorax is uncommon. The heart is acutely enlarged, the rate is rapid, and a gallop rhythm and/or premature contrac-

tions may be present, atrial fibrillation is rare. The blood volume is increased, generally with a larger increment in red cell mass than is seen in left heart failure. The cardiac output may be reduced, normal, or even increased. The distinction between this group and the group with chronic progressive cor pulmonale to be discussed in the next section, may be obscure during an attack of acute bronchitis or bronchopneumonia. However, a considerable degree of elevation in arterial blood P_{CO_2} and content, and a considerable degree of polycythemia, suggest that the patient belongs to the chronic progressive group rather than to the group presently under consideration.

With vigorous and adequate treatment, the attack subsides and cardiac compensation is temporarily restored.

Chronic Progressive Cor Pulmonale

The typical form is the "Ayerza syndrome," "cardiacos negros," a steadily progressive state of right heart enlargement and failure, occurring in profoundly anoxic and usually hypercapneic cases of chronic obstructive emphysema, with marked polycythemia, elevated hematocrit, markedly increased blood volume and advanced systemic congestive failure. Cardiac output is increased, sometimes to twice normal, the so-called "high output failure."

An important feature of these cases is the severely obstructive nature of the pulmonary insufficiency, in which poor mixing of respiratory gases is a factor both in the hypoxia and CO_2 retention.

Emphysema and Independent Left Ventricular Disease

A not uncommon combination is emphysema and independent left ventricular disease such as coronary arteriosclerosis leading to myocardial infarction. Actual or latent left ventricular failure aggravates the patient's pulmonary symptoms and he may become a totally incapacitated cardiopulmonary cripple.

Treatment of Cor Pulmonale Occurring in Pulmonary Emphysema

Since cor pulmonale with congestive heart failure occurs as one of the end stages of chronic pulmonary emphysema, its clinical

management is usually difficult and complex At this stage, multiple bodily systems are involved—pulmonary, cardiac, renal, cerebral; treatment should therefore be thought of in the broadest terms

Pulmonary

The fact that cor pulmonale is always heart disease secondary to lung disease must be kept constantly in mind, and every effort made to improve all aspects of pulmonary function Such therapy has been covered in ample detail in other chapters, so that the following brief outline should suffice.

AIR PASSAGES

Patency of airways is obviously all-important for ease of ventilation and for even distribution of inhaled air to perfused alveoli. Bronchodilators, especially the vaporized sprays, and antibiotics for chronic infection with exudate, are probably the most useful of all procedures Surface tension-reducing aerosols, postural drainage, mechanical aids to cough may also be of value. Whether the so-called expectorants have more than placebo value is problematical An uncommon but critical situation is that of acute asphyxia from retained exudate, in which mechanical suction or bronchoscopy is life saving

MECHANICS OF VENTILATION

The various aids to breathing may be alluded to briefly: breathing exercises, postural maneuvers such as the head down position, supporting abdominal belts In the advanced stages of cor pulmonale with failure, these are usually not of great help Abdominal belts, particularly, are uncomfortable when there is circulatory congestion with liver enlargement. Pneumoperitoneum, in the writers' experience, has been worse than useless in these cases

The important question of mechanical respirators will be considered in the next section

RESPIRATORY GAS EXCHANGE

The dominant importance of hypoxia in the pathogenesis of cor pulmonale has been sufficiently presented in the early part of this chapter Of equal urgency is the relief of hypoxia as one of the basic features of treatment Usually some form of direct oxygen therapy will be needed, especially in the more acute phases of decompensation, in addition to the procedures already mentioned above for improving pulmonary function The various specific types of oxygen therapy, the levels of arterial hypoxia for which each is indicated, and other details of treatment are given in other chapters and need not be further reviewed here Frequently, after pulmonary and cardiac compensation has been restored, continued oxygen becomes unnecessary, but advanced states may require continuous inhalation therapy

CO_2 elimination may also become a problem in advanced stages of pulmonary insufficiency Physiologically, CO_2 output is directly proportional to the amount of "alveolar" ventilation (which is total ventilation minus "dead space" ventilation) Normally the respiratory center provides a sensitive regulation of breathing, the smallest retention of CO_2 with rise in arterial blood P_{CO_2} and drop in pH resulting in a compensating increase in minute ventilation This stimulus-response relationship may continue to function normally even in quite advanced ventilatory insufficiency Eventually, however, with decrease in breathing capacity and progressive distortion of alveolar ventilation and capillary perfusion, hypoxemia becomes more severe, CO_2 is retained, and arterial P_{CO_2} becomes increased As a result of this, two additional physiologic adjustments occur (1) A diminution in sensitivity of the respiratory center which accompanies an increase in arterial blood P_{CO_2}, this diminished sensitivity to the prime respiratory stimulus augments the contribution of hypoxemia to the total respiratory drive If this state of severe hypoxemia and hypercarbia is not promptly relieved, permanent depression of the respiratory center may ensue (2) The increase in arterial blood P_{CO_2} in turn stimulates a retention of bicarbonate by the kidney,

which tends to keep blood pH normal, but which may in turn perpetuate or increase the increment in blood P_{CO_2} by *further* depressing the respiratory center.

Biologically these changes constitute both a good and an evil, one of the points in disease where homeostasis and "hyperexis" (the "excess response") converge. It is a good because the high P_{CO_2} enables metabolic CO_2 to be eliminated with relatively small total alveolar ventilation, it is an evil because a vicious cycle may be set up reducing progressively the respiratory stimulus, with P_{CO_2} increasing to the level of CO_2 narcosis.

Therapeutically, the use of oxygen in such situations has to be managed most carefully, because rapid and full oxygenation of the blood will remove the anoxic stimulus to respiration, precipitating acute CO_2 retention and CO_2 narcosis, sometimes within a few hours

It is in these situations characterized by CO_2 retention that mechanical respirators will be most useful, or even life-saving Unfortunately, it is not possible to define concrete criteria for the use of mechanical respirators. However, some index may be gained from an analysis of blood gas CO_2 and pH. Thus, when the arterial *CO_2 content exceeds 70 volumes per cent (30mM) or when the* arterial blood P_{CO_2} exceeds 65 mm. Hg, or the venous plasma CO_2 content exceeds 80 volumes per cent, and especially if there is a *considerable uncompensated respiratory acidosis* as indicated by an arterial pH below 7 32, artificial respiration should be used, either continuously, or in repeated applications of ½ to 3 hours each, throughout the day and night. A further indication exists if a preliminary trial of spontaneous oxygen breathing results in a sharp additional rise in CO_2

In most instances of CO_2 retention, an intermittent positive pressure respirator such as the Bennett or Emerson apparatus will be adequate A special distinction should be drawn between the respirators which provide automatic cycling, both for expiration and inspiration, and those IPP (inspiratory positive pressure) apparatuses which require the patient's own inspiratory effort to trigger the inspiratory cycle The use of the latter for the administration of 100 per cent oxygen *to patients in far advanced pul-*

monary failure and respiratory acidosis may be dangerous, because a few breaths of oxygen may so eliminate the anoxic stimulus to respiration that the patient stops breathing altogether and may asphyxiate In such cases, the use of compressed air, or a tank with 25 or 30 per cent oxygen, may avoid this complication

The value of repeated analyses of arterial blood for oxyhemoglobin saturation, P_{CO_2} and CO_2, in tracing the evolution of cor pulmonale needs no emphasis It is, however, noteworthy that similar analyses during and shortly after treatment with a respirator provide an index to the efficacy of treatment and a guide to optimal time for the discontinuance of this type of therapy

In the most severe cases, fully controlled respiration in the Drinker respirator, for periods of 12 to 48 hours, may be necessary This is a procedure requiring most careful and continuous care, together with repeated measurements, once or twice daily or oftener, of arterial blood CO_2, P_{CO_2}, pH, and oxyhemoglobin saturation

In the writers' clinic are several patients who have been rescued repeatedly, over the past three years, from apparently irreversible CO_2 retention by the use of the Drinker respirator

Heart, Blood, and Circulation

When the right heart failure, and the congestive state, is manifest, digitalization is indicated, since it has been shown, just as in congestive heart failure of other etiologies, that ventricular emptying is thereby improved and stroke volume increased The usual indications for both initial and maintenance therapy prevail

The polycythemia and hypervolemia of cor pulmonale in failure tends to return toward normal with relief of hypoxia and improvement in the circulation, but repeated phlebotomies accelerate the process and are often beneficial Repeated phlebotomies of 500 cc each are better tolerated than larger amounts In chronic cases, with recurrent polycythemia, blood may be removed, for extended periods, at intervals of one to two months Phlebotomy is indicated only if there is evidence of increased blood volume, *i e*, the congestive state; polycythemia alone, of moderate degree,

is not in itself an indication With return of blood volume and hematocrit toward normal, and improvement in blood oxygenation, cardiac output in the "high output failure" cases also drops to normal values

Mercurial diuretics and low sodium diets are employed as in any right-sided congestive heart failure

The use of Diamox appears to have a special place in treatment of chronic cor pulmonale This drug in doses of 250 to 500 mg daily, not only serves to maintain blood bicarbonate at lower levels, but also appears to lessen the tendency to edema formation It may be continued in the 250 to 500 mg. daily dosage for many months Larger doses raise the problem of a clinically significant superimposed metabolic acidosis, as well as potential inhibition of erythrocyte carbonic anhydrase

Finally, brief emphasis may be directed to the broad difference in management and prognosis between the cases of acute cor pulmonale (*mentioned above under Clinical Forms of Cor Pulmonale*), and the cases of chronic cor pulmonale, or "Ayerza syndrome " In the acute form, as the precipitating mechanism is relieved, symptomatic recovery is generally rapid and complete, and continued cardiotonic treatment may be unnecessary. On the other hand, in chronic cor pulmonale, following recovery from an episode of heart failure, prolonged therapy, in line with the principles outlined above, is mandatory

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Chapter 16

SURGICAL PROCEDURES IN PULMONARY EMPHYSEMA

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INTRODUCTION

In the surgical consideration of hypertrophic pulmonary emphysema, one must accept palliation rather than cure as the measure of success. Occasionally dramatic results may be observed following the excision of large blebs or bullae which have compressed adjacent lung tissue. Some degree of protection of the patient may be achieved by obliteration of such spaces in the presence of hemorrhage into blebs or bullae or when recurrent or chronic pneumothorax has resulted from leakage of air from these abnormal areas.

When improvement in respiratory function is desired, the proper selection of patient and procedure may be most difficult. Indeed, some surgeons have felt that surgical measures should be confined to the treatment of the complications of emphysema, such as pneumothorax, hemorrhage, or empyema. Nevertheless, experience has shown that there are certain patients who can derive sufficient benefit to warrant definitive surgery being considered. Such patients should have an adequate trial on a complete medical regimen, including in selected cases avoidance of smoking, control of allergens and industrial toxic products. Infection of the respiratory tract must be eliminated if possible by parenteral and inhalational administration of proper antibiotic drugs. Postural drainage may be of benefit, especially if an element of bronchiectasis is present. Improvement in ventilation and in the use of functioning lung tissue may be effected by use of bronchodilator drugs,

steroid therapy, administration of oxygen (at times with positive pressure) Instruction in proper posture and breathing exercises may be most beneficial. The use of abdominal belts and of pneumoperitoneum may play a part in the rehabilitation program Finally, significant rightsided heart strain or failure must be corrected by rest, oxygen, therapy, digitalis preparations, low salt diet and diuretic drugs

Abbott and his colleagues (1953) reported a clinical study of 294 patients with pulmonary emphysema in varying stages and with varying degrees of disease. They found that 267 patients had evidence of bronchospasm Among the associated conditions, tobacco irritability was noted in 214 patients, and suppuration in 209. It is of interest that on a medical regimen considerable benefit was obtained in 17 patients in whom organic damage was minimal or absent

If after adherence to a medical program for four to six months a patient continues to have significant dyspnea or cough, or evidence of progression of his emphysema, one may be justified in evaluating him with regard to possible surgical benefit.

Special Diagnostic Measures

Radiography

In addition to standard roentgenograms in various projections, and fluoroscopy, one may occasionally gain supplementary information from laminograms The extent and number of blebs and bullae may be delineated sufficiently to indicate more exactly the volume of lung involvement Bronchography has been helpful in some cases, especially if a localized bronchial obstruction is suspected, as from stenosis or foreign body, or if bronchiectasis is thought to be present Dugan and Samson have used bronchography to estimate the amount of compressed functional lung tissue which will re-expand following excision of giant blebs or bullae On the other hand, some prefer to avoid bronchography whenever possible, because of obstruction of smaller air passages and functioning alveoli by iodized oil Also the interpretation of subsequent radiographic studies is at times difficult as a result of

retained contrast material Of some interest, however, has been the occasional observation of improved symptoms following use of iodized oil in a lung containing blebs or bullae It is thought that the material may have blocked the check-valve orifices of the bronchi into the distended air spaces With the development of better water soluble materials, some of the objections to bronchography will be overcome (Fig 16 1a and b)

Angiocardiography has been used to advantage by Abbott, Miscall and others in mapping a lung involved in bullous emphysema The relative absence of vascularity in blebs and bullae makes this method of visualizing radicals of the pulmonary artery effective in estimating the areas of maximal involvement, when excisional therapy is under consideration (Fig 16 1c and d) Miscall favors this procedure over bronchography as being simpler, safer, and more accurate

TECHNIQUE

This study may be accomplished in adults without anesthesia and in the sitting position A large bore needle, preferably a 12-gauge Robb needle, is introduced into an antecubital vein after infiltration of the tissues with one per cent procaine The patient is positioned in the anteroposterior projection before a stereoscopic changer, which is loaded with 14 x 17 inch film One second after the completion of the rapid injection of 50 cc of concentrated organic iodide contrast materials* the first film is exposed and immediately thereafter the second film is shifted into position and exposed This technique affords a very simple means of obtaining two films during the passage of the contrast material through the pulmonary arteries A second injection may be performed if necessary

If rapid seriographic apparatus employing large size film is available, continuous exposures every half second or so afford a better representation of the vascular anatomy, arterial and venous of the lung Unfortunately, most equipment available at the present employs small size films, thus limiting the area which can be studied

* In our experience 70 per cent Urokon (R) has been satisfactory

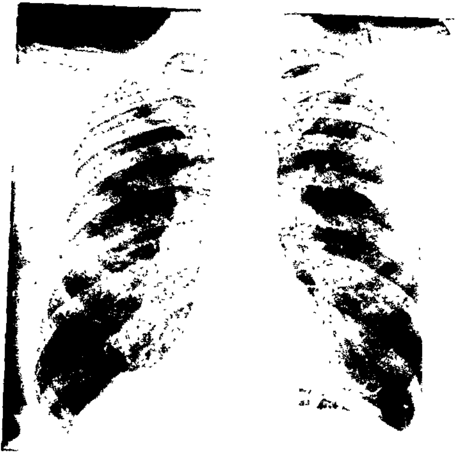

FIG 16 1.

(A) Standard posteroanterior roentgenogram of chest revealing diffuse hypertrophic and bullous emphysema of both lungs Note the increased radiolucency of the enlarged lung fields and particularly in the right midlung area The heart is not enlarged

Abbott has considered fluoroscopy as "the most important tool for the proper evaluation and early diagnosis of pulmonary emphysema " Differences in function of the leaves of the diaphragm, displacement of the heart and mediastinum during expiration, rapidity and uniformity of expiration, intensity and *distribution* of vascular radicals are hints as to the severity and localization

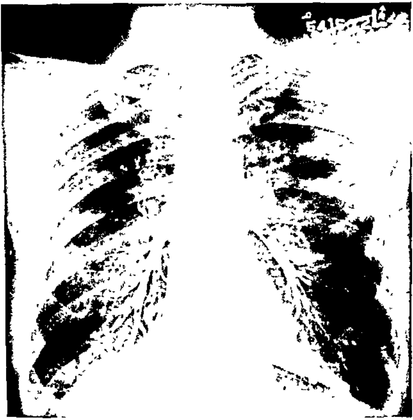

FIG 16 1 (*cont*)

(B) Bronchogram revealing slight degree of cylindrical bronchiectasis in basilar segments of lower lobes, especially on right There is a relative absence of peripheral bronchial filling in the lateral portion of the right upper lobe

of emphysematous changes suitable for surgical procedures The postoperative examination is helpful in the appraisal of operative benefits in respect to ventilation

Bronchoscopy

The value of this procedure in evaluating a patient for surgery lies in the exclusion of foreign bodies, stenosis or extrinsic pressure

FIG 16 1 (*cont*)

(C) Angiocardiogram at 3 seconds reveals filling of the peripheral pulmonary [illegible]

exposure of the film

in the etiology of a localized emphysema The presence and degree of bronchiectasis is of real importance in the estimation of the scope and risk of surgery, as well as in the probability of achieving lasting benefits Pre-operative ventilation may be improved, thus

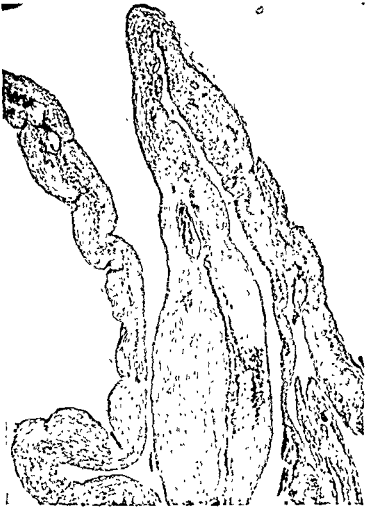

Fig. 161 (cont.)

(D) Photomicrograph of portion of bulla shown in roentgenograms. The lung adjacent to the large air space is composed of dense fibrous tissue in which only a few recognizable remnants of pulmonary parenchyma can be seen. Some anthracosis is present. The spaces are lined by inconspicuous flattened cells. (H & E stain, 45 ×)

increasing the cardiopulmonary reserve of the patient Specimens of material aspirated during bronchoscopy should be studied by culture to indicate type and sensitivities of existing bacterial flora, and to exclude tuberculosis or fungus infection, should these be possibilities

Thoracoscopy

This special technique has been recommended by Head and Avery in preference to thoractomy as a means of localizing blebs or bullae and adhesions involved in the production of spontaneous pneumothorax They believe that the pleural symphysis which results following thoracotomy may reduce further the vital capacity of a markedly emphysematous lung, although such pleurodesis is often effective in preventing recurrence of the pneumothorax D'Abreu and Brock have also recognized the value in such cases They believe that the appearance of the surface of the lung following spontaneous pneumothorax will enable the surgeon to decide whether the best management should be by surgical exploration or by chemical pleurodesis Brock favors the latter in the presence of generalized emphysema, porous lungs and apical bullae with localized scarring Miscall, Clagett, Cooke and others, however, have not advocated thorocoscopy as a means of deciding on thoracotomy in such cases

The introduction of a needle into blebs or bullae in order to determine whether elevated pressures exist carries definite dangers The occurrence of near fatal pneumothorax as a result has been mentioned by D'Abreu, Miscall and others Burnett believes such information to have insufficient diagnostic value to warrant the risk

Cardiopulmonary Function Tests

Specialized studies of the functional reserve of the heart and lungs are of real value in determining the risk of surgery, the areas of maximal dysfunction of living tissue and the degree of benefit which may follow surgical therapy Although perhaps not essential in the selection of some cases with very localized involvement, the values for vital capacity, maximum breathing capacity

and residual air of the lungs, and oxygen saturation of the arterial blood afford some objective means of measuring therapeutic benefits Some authors have advocated wider use of bronchospirometry, recognizing its advantages in the study of lungs with an irregular distribution of emphysematous changes

Biopsy

In complicated cases, a specific tissue diagnosis by microscopic examination is of inestimable value If this can be achieved with minimal risk or morbidity, the knowledge thus gained can be of positive value in therapy and prognosis In certain patients emphysema may be associated with pulmonary fibrosis of considerable degree In others, the roentgenogram may suggest possible silicosis, sarcoidosis, metastatic malignancy, or an unusual type of infectious process, in association with emphysema Daniels described a simple method of biopsy of the scalene lymph node which has been found helpful in establishing diagnoses Shefts and associates reported on the diagnosing of histoplasmosis and sarcoidosis by such means

Direct biopsy of lung tissue has been advocated by Effler and associates in preference to needle biopsy They have used this technique for over five years in patients with undiagnosed diffuse pulmonary disease or in patients with possible mediocolegal aspects, as related to occupational disease There has been one death among 65 patients so studied, and this mortality was the result of a coronary occlusion occurring on the fifth postoperative day This method has been employed to advantage by the author as well (Fig 162)

TECHNIQUE

Following the administration of pre-operative medication, the pharynx and pyriform sinuses are treated with a topical anesthetic An endotracheal tube is inserted after induction of anesthesia by 50 per cent oxygen and 50 per cent nitrous oxide Small doses of Pentothal Sodium may be administered intravenously The patient may be supine with the operating table tilted with the head elevated, if desired Positive control of respiration is achieved

FIG 16 2 Standard posteroanterior projection of chest during inspiration There is a fine reticulation through both lungs including larger radiolucent areas, suggesting areas of fibrosis and emphysema The displacement of the mediastinum and cardiac silhouettes into the left hemithorax suggested inflammatory disease, particularly since increasing dyspnea began four years previously subsequent to an attack of penumonia At time of operation the lung tissue was firm and pale with a cobblestone appearance from multiple tiny blebs A biopsy from the lingular portion of the left upper lobe revealed fibrosis of lung and bronchiectasis.

by the anesthetist The site of exploration is usually either in the lateral or anterolateral chest and this area may be infiltrated with one per cent procaine before a 15 cm skin incision is made. The lung is exposed through the fourth or fifth interspace, by employing a small rib-spreader Often the most accessible site for biopsy is the edge of the lung at the fissure, provided a representative biopsy could thus be obtained. A row of hemostatic mattress sutures of fine chromic catgut material is placed across

the site of biopsy before resecting a specimen Care is taken to secure all bleeding points and air leaks The lung is kept expanded during closure of the chest and simple underwater drainage or low suction drainage employed for 24 to 72 hours The specimen may be subdivided for microscopic study, culture and even chemical investigation

DEFINITIVE SURGICAL PROCEDURES

As indicated in the introductory remarks, there are two types of surgical approach in the treatment of emphysema The one deals primarily with specific complications or urgent problems arising as a result of hypertrophic emphysema In this category may be listed spontaneous pneumothorax and tension bullae or cysts Of increasing interest also is the obstructive lobar emphysema observed in infants and children, which often demands emergency surgical management

The second type of surgical approach is centered primarily at means of improving pulmonary function Some of the theories underlying certain procedures are controversial and, to a certain extent, some of the techniques are experimental This is particularly true of operations designed to help patients with advanced diffuse hypertrophic emphysema of both lungs On the other hand, a direct approach with respect to decompression or excision of large blebs and bullae has been rewarding in many instances

Diffuse Hypertrophic Emphysema

Freund described an operation which was designed to relieve intrathoracic pressures associated with diffuse emphysema Resection of the cartilages articulating with the sternum was performed in order to render the fixed and rigid thorax more flexible Unfortunately, the released lung continued to distend and the thorax stabilized in an even more expanded state Needless to say, these patients derived no benefits and often were more incapacitated Although Huet and Blamoutier thought the Freund operation might be helpful in certain selected cases with asthma, the procedure has been abandoned

The significant bronchospasm observed in patients suffering

from asthma led to a trial of surgery of the autonomic nervous system. In 1923, Kummell resected dorsal sympathetic ganglia and later combined a unilateral vagal section Kappis in 1924 claimed some successes following resection of the right vagus nerve below the recurrent laryngeal nerve. In 1928 Leriche and Fontaine reported some encouraging results following resection of the stellate ganglia for asthma. In this country, Phillips and Scott reviewed the experience with autonomic surgery and advocated surgery of the vagus nerve for treatment of asthma. More recently, Carr and Chandler reported on the use of dorsal sympthectomy for the control of asthma, and Rienhoff and Gay and Blades, Beattie and Elias revived interest in vagal plexus denervation at the hilus Blades also stressed the importance of stripping away the peribronchial and perivascular tissue, as well as division of the pulmonary ligament Late follow-up studies by the latter techniques as employed by various surgeons in America reveal discouraging results, although occasional lasting benefits could be observed

In the treatment of emphysema, Abbott and Crenshaw independently have included autonomic denervation as part of their program Abbott has employed dorsal sympathectomy through the sixth ganglion and including the stellate ganglion only if the procedure is unilateral On the right side the entire thoracic vagus nerve is resected below the recurrent laryngeal nerve, whereas on the left side he relies on hilar denervation and removal of the adventitia from the pulmonary artery Following disappointing results when autonomic nerve surgery alone was employed, Abbott now combines nerve surgery with excision of blebs or resection of bullous areas. He employs atropine among other autonomic drugs in a effort to evaluate the patients preoperatively, noting the degree of improvement in pressure in the pulmonary artery and in improved ventilation as a result of relief of bronchospasm He concludes that surgery has failed to benefit patients with fixed emphysema and with little remaining useful lung tissue In a report on 67 surgical cases in 1953, he claimed good results in 21 patients with bullous or mixed types of emphysema On the

other hand, only 7 or 9 were helped among 46 patients with diffuse hypertrophic emphysema

Crenshaw has presented a theory that the primary process causing progressive degeneration of pulmonary tissue is on a vascular basis. He believes that sclerosis of the bronchial arteries may effect a loss in elasticity and thinning of alveolar walls. Cudowicz and Armstrong have also observed sclerosis of the bronchial arteries in patients with emphysema. Crenshaw also includes as important features the detrimental effects of bronchospasm and of large blebs and bullae. All these factors are considered in his proposed surgical approach which he describes, as follows: "An open thoracotomy is done. Degenerated lung is removed by segmental resection or lobectomy. Subpleural bullae and blebs are removed by clamp resection. Smaller bullae and blebs are treated by individual mattress sutures. As far as possible, all air leaks are controlled. Complete vagal denervation is accomplished by severance of branches at the hilum, including those from the left recurrent laryngeal nerve. Perivascular and peribronchial tissues are dissected and the inferior pulmonary ligament is severed (Blade's technique). The sympathetic chain is removed from the third through the ninth ganglion, including the splanchnic nerves. The parietal pleura is removed from the chest wall. Irritative sterile talc is powdered over the visceral pleura. When the chest is closed, two large intercostal tubes are inserted to which regulated suction is applied as soon as the patient is returned to his room." In 1952, he reported 11 cases so treated with one death, and a follow-up period of from five weeks to two years. All had failed to improve on a full medical regimen, and were considered poor risks for surgery. All were dyspneic and some orthopneic and cyanotic. He noted, as have others, the immediate improvement in ventilation as soon as the chest cavity was opened and compression of the lung relieved by escape of bullae into the wound.

Of importance was the management during the postoperative period, which he described as being stormy. The difficulty in suturing degenerated lung led to air leaks for which continuous suction was required. Pain limited the respiratory excursions and

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effective cough. Two patients required positive pressure oxygen therapy with a Bennett valve temporarily. Nevertheless, improvement was marked in three patients with bullous disease Four cases with resection of degenerated lung ("cotton-candy lung") had slower improvement and three with diffuse hypertrophic changes required up to four months before slow improvement was noted.

Dugan and Hardy agree with Carter in that the problem in emphysematous patients is primarily ventilatory and not vascular They do not favor pleurectomy and poudrage therefore, and believe that significant systemic-pulmonary anastomoses thus initiated might well increase the work load of the left heart. They point out that emphysema is a progressive process and that it is not slowed nor is lung regenerated by poudrage. They also believe that "denervation operations (autonomic ablation) have nothing to offer in the surgery of pulmonary emphysema"

In reference to poudrage, Blades has recommended the use of sterile talc for effecting pleural symphysis in the treatment of spontaneous pneumothorax, citing evidence that shows no diminution in pulmonary function to follow this procedure (Paul, Beattie, and Blades) This is in contrast to the contention of Head and Avery that pleural symphysis following thoracotomy in emphysematous patients might produce further reduction in lung function

Localized Blebs and Bullae

Perhaps the most frequent application of surgery in the treatment of emphysema has been in the treatment of blebs and bullae Although terminology has been confusing in respect to cysts, cyst-like spaces, cystic disease—acquired and congenital, and blebs and bullae, there have been some efforts made to clarify the classification Clagett has differentiated cystic lesions into two chief types, those arising from the bronchial tree and those of alveolar origin The former usually have an epithelial lining and may contain air or fluids alone or in combination. The cysts of alveolar origin are blebs, bullae and pneumatoceles. According to Miller, a bleb arises from rupture of the subserous layer of the

pleura and formation of a space between pleura and pulmonary tissue by air escaping from ruptured alveoli. Bullae and pneumatoceles are located deeper in the lung, the former being produced by continuous rupture of dilated alveoli into one another. Maier has defined the pneumatocele as a hyperinflated intrapulmonary cavity produced by the marked distention of a defect in the pulmonary parenchyma. Isolated blebs or bullae do occur in lungs essentially free of emphysema. However, in the badly degenerated lung of the patient with advanced emphysema, there are generally present a combination of these cysts of alveolar origin. The following surgical discussion will be limited to this type consequently.

Aspiration of air from these cystic lesions by needle has been shown to be both ineffective for decompression and dangerous because of the risk of inducing a tension pneumothorax. Clagett, Dugan and Samson, and others have at times employed suction with a needle introduced into a space which could not be clearly defined as huge bleb or pneumothorax. This measure has been used usually as a temporary measure to relieve desperate symptoms while preparing for thoracotomy.

The use of catheters for continuous drainage of pulmonary cysts by Lilienthal and Croswell and King led to partial decompression and relief of dyspnea and cough. Subsequently, Head and Avery recommended intracavitary suction by the Monaldi method in patients too ill for thoractomy and yet severely incapacitated by respiratory insufficiency.

TECHNIQUE

After accurate localization of a large bleb by roentgenograms and fluoroscopy, the overlying site on the chest wall is infiltrated with one per cent procaine. By extrapleural exploration, the surgeon determines whether pleural symphysis is present over the bleb. Since there generally are free pleural surfaces, a gauze pack is inserted in the extrapleural space to promote adhesions between the surface of the cavity and the parietal pleura. At a second stage several days later, the pack is removed and the wound is again allowed to heal. Subsequently, a thoracoscope is introduced di-

rectly into the bleb with minimal risk from pneumothorax. Pressure readings and even biopsy may be obtained A multiple fenestrated catheter is next introduced into the cavity and simple underwater drainage employed for up to three days If air continues to leak, suction of 10 to 20 cm of water pressure is instituted, in order to decompress and collapse the cavity. The program generally requires from one to three weeks. This type of management is not satisfactory for epithelial-lined cysts which should be excised As a variation in the technique, some surgeons have introduced a catheter into the cavity by means of a trocar at the time of removing the gauze pack Head and Avery have claimed success with this method in selective cases as have Cooke and Schaff, Mead, and Mosko and Baugher.

Thoracoplasty of the chest wall overlying cysts, blebs and bullae has been tried, following the suggestion of Eloesser, but without success. Crushing of the phrenic nerve has been advocated by Allison as a means of relieving the dyspnea associated in some patients with giant bullous cysts.

During the past several years, there have been increasing reports favoring excision or resection of lung tissue in the treatment of blebs and bullae This approach depends on many factors, the main one being the general condition of the patient Further, if the air spaces are asymptomatic, if they measure 5 cm. in diameter or less, if they are multiple and bilateral, or if there is an underlying extensive bilateral emphysema, one would hesitate to carry out definitive surgery It should be kept in mind, however, that a tiny solitary bleb can suffice to produce a spontaneous pneumothorax, which in itself demands positive measures. Fortunately, hemorrhage or infection in these spaces are rare, mainly because of the poor vascularity and alveolar origin In bullae, it is not uncommon to be able to identify slit-like openings in a bronchial wall which act as check valves, and thus produce continued over inflation of the cystic space (Hayashi, Allison). At times huge bullae can develop as a result of bronchial obstruction

Removal of blebs is simply effected by unroofing the air space beneath the pleura by open thoractomy Inflation of the lung by the anesthetist and filling the depression of the bleb with saline

solution may reveal a site of leakage At times a suture of fine chromic catgut will control the escape of air If the bleb wall is epithelialized, it must be removed so that obliterative healing can occur If the cystic space is large, the walls may be approximated by sutures of chromic catgut in order to eliminate dead space and to prevent subsequent air leak Although several blebs may be handled in this manner, if a segment or entire lobe are involved in blebs and bullae, often it is better to perform a resection of the involved lung A catheter is left in the pleural space for under-water or low pressure suction drainage Antibiotic drugs may be left in the pleural space when the chest is closed and are administered parenterally for several days after operation A combination of penicillin and streptomycin is usually satisfactory, although the newer mycins may be preferred

At times decompressive measures combined with excisional therapy of large blebs or superficial bulla in stages may be undertaken in desperate efforts to improve failing respiratory function in young patients with extensive emphysema The following case report is one in which Monaldi type of intracavitary drainage was performed in two stages, as well as excision of a multiloculated bulla, with subsequent brief periods of symptomatic relief Additional measures such as thyroid depression, pneumoperitoneum, and steroid therapy were also ineffective in preventing the relentless progress of emphysema and pulmonary fibrosis

CASE F D

A 32-year-old white married woman (#100857) suffered from progressive incapacitation from pulmonary emphysema and fibrosis, the symptoms of which began in 1945 At this time she had a bilateral spontaneous pneumothorax followed by bilateral empyemas The infections were controlled with some difficulty and drainage was required on the right side (fig 16 3a) Some improvement was noted with breathing instruction in 1952 but following several bouts of pulmonary infection the patient had right heart failure which responded to rest oxygen and digitoxin In November 1953 the patient had a first stage operation for cavernostomy of a bulla of right upper lobe At this time the pleura was packed with gauze and five days later packing was removed and a trocar was inserted into the bulla through which a number 22 French catheter was placed Suction drainage was applied The decompression of the bulla afforded temporary symptomatic improvement (fig 16 3b) A medical ablation of the thyroid gland was

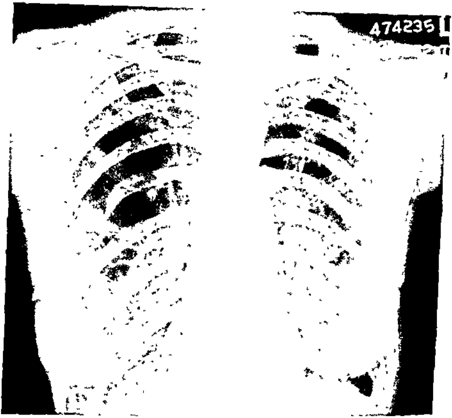

Fig 16 3

(A) Standard posteroanterior roentgenogram of chest of young woman revealing extensive bullous emphysema and fibrosis of both lungs. The surgical defect in the right eighth rib was associated with a drainage of an empyema subsequent to a spontaneous pneumothorax The patient also had simultaneous spontaneous pneumothorax with subsequent empyema on the opposite side Note the marked decrease in lung markings in the right mid and upper lung fields

carried out with RAI in January 1954 Subsequent to this, pneumoperitoneum was carried out without lasting benefit in February 1954 In July 1954 a large bullous area deep to the seventh rib on the right was unroofed and the bronchial openings closed with approximation of the walls of the space (fig 16 3c) Although only partial correction was possible because of the extremely extensive bullous degeneration and actual destruction of lung with fibrosis, there was significant symptomatic improvement for eight months During this period of time she was at home and able to tolerate increasing periods of time without oxygen

FIG 163 (*cont.*)

(*B*) Chest film subsequent to a two-stage cavernostomy and intracavitary closed suction drainage (Monaldi) of bulla in right apex

therapy There was a rapid regression subsequent to this, necessitating almost continuous hospitalization subsequently and in December 1955 a continuous administration of oxygen at 7 to 8 liters per minute was necessary Her course illustrates the progressive deterioration which can be modified only temporarily by surgical procedures in some patients

The surgical management of bullae may require more extensive resection than is necessary with blebs In general, they can not be excised because of the absence of cleavage planes

Abbott and associates have described a technique of wedge resection over a Potts' coarctation clamp thus minimizing extrav-

chapters by Barach and Beck, support the argument for permitting expansion of remaining lung and against the use of space fillers.

The following case report is a representative example.

CASE K C

This 66-year-old white male (#122990) had first noted dyspnea on exertion about 16 years prior to admission Approximately 10 years before admission he had primary atypical pneumonia subsequent to which there was a much more rapid progression of dyspnea A few years later he was told he had emphysema which involved the right lung primarily (fig 16 4a) All medical management, including a course of cortisone had failed to improve him with the exception of

FIG 16 4

(A) Pre-operative posteroanterior roentgenogram of chest with barium in esophagus Note radiolucency and absence of bronchovascular markings in the right upper lung field in particular

oxygen therapy Bronchoscopy revealed some narrowing of the right main bronchus Bronchospirometry indicated bilateral moderate emphysema was present In view of progressive deterioration clinically, a right upper lobe lobectomy was performed on July 1, 1953, by Dr Frank Berry At operation the pleural cavity was obliterated by dense, old avascular adhesions as were the lung fissures The right upper lobe was enormously distended, occupying the upper three-quarters of the chest, remaining distended in both phases of respiration The bronchus to the upper lobe was greatly thickened and narrowed at its entrance into the anterior segment The middle and lower lobes did not expand

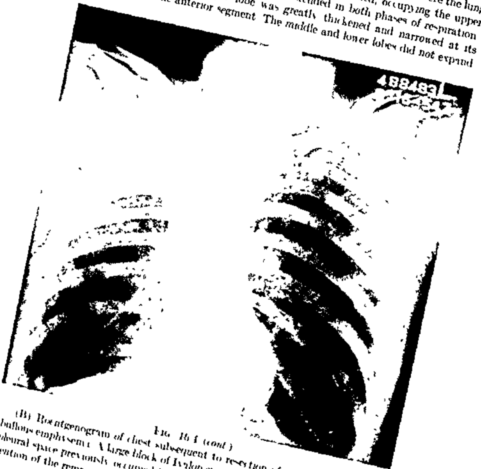

FIG. 16 4 (cont.)

(B) Roentgenogram of chest subsequent to resection of right upper lobe for bullous emphysema A large block of Ivalon sponge was tailored to fill part of the pleural space previously occupied by the upper lobe in order to restrict the distention of the remaining right middle and lower lobes

Fig. 16.4 (*cont.*)

(C) Left lateral projection of chest revealing the Ivalon pack in an apical position. The position of the oblique fissure between the remaining right middle and lower lobes indicates that there is an increase in volume of these lobes as result of emphysema.

well and contained several bullae. Function did improve after removal of the upper lobe, however. A block of Ivalon sponge was placed in the apical region to prevent over distention of the emphysematous middle and lower lobes (fig. 16.4b and c). Despite a period of improvement, the patient developed evidence

FIG 16 4 (*cont*)

(D) Overexposed anteroposterior projection of chest reveals a moderate angulation of trachea to the right with evidence of kinking of the bronchi to the middle and lower lobes, particularly to the latter It was felt that the Ivalon pack perhaps prevented overdistention of remaining lung tissue but also contributed to the development of partial obstruction to the bronchi to the middle and lower lobes, as determined by clinical signs and fluoroscopy

of obstructive emphysema in the right middle lobe and right lower lobes Although it was felt that there had been a logical basis for trying to prevent overdistention of the residual lobes partial angulation of the bronchi produced in effect obstructive emphysema with further decrease in ventilatory function on

this side (fig 16.4d) Additional resection of lung tissue was not considered reasonable and despite continued use of medical adjuncts, the patient died five months following the lobectomy. At autopsy there were noted severe sclerosis of the bronchial arteries and severe bronchomalacia In addition there was severe progressive bolus emphysema with definite obstructive features, undoubtedly the result of the bronchomalacia It could not be stated positively whether the sclerosis of the bronchial artery had a direct degenerative effect on the pulmonary parenchyma itself as claimed by Crenshaw, and Cudowicz and Armstrong

The postoperative course with excisional or resection therapy may be difficult, and close observation is demanded of the medical staff In addition to administration of antibiotics, expectorants and bronchodilator drugs may be required Oxygen therapy, by catheter, tent or mask, is a necessity. At times intermittent positive pressure is very helpful, as well as use of oxygen and helium Oxygen therapy may be needed for several weeks or even longer. The serum electrolytes and blood pH may deviate widely from normal, and corrective measures may be indicated. Intravenous fluids are administered sparingly and usually the patient can take fluids by mouth later in the day of operation. The control of pain is important in reducing splinting and in permitting greater cough- ... most instances

be given to suction drainage apparatus, so as to note kinking of tubes or mechanical failures Expansion of residual lung should be maintained so as to afford maximal respiratory function Also, effusion should be kept to a minimum for the same reason and in order to diminish the chances of empyema developing In general, drainage catheters may be removed in from two to five days Early ambulation is to be encouraged if the condition of the patient is satisfactory. It is most important to emphasize the close coordination of the medical and surgical teams during the immediate pre and post-operative periods of these patients

Spontaneous Pneumothorax

The collapse of a lung as a result of air leaking from a bleb or bulla may be gradual or sudden. In the later instance, the patient

may have chest pain, cough, dyspnea, apprehension and cyanosis. In gradual or chronic pneumothorax, symptoms may be absent or minimal, being evident only on exertion. The symptoms depend on the extent of collapse in part, and may be very severe in simultaneous bilateral collapse.

Physical examination and standard roentgenogram of the chest may suffice to establish the diagnosis, although there are patients with mild symptoms who have huge blebs simulating a pneumothorax. For this reason use of a needle for aspiration should be carried out with some caution. If the spontaneous pneumothorax is greater than 20 per cent, re-expansion by insertion of a blunt metal cannula or rubber catheter into the second interspace anteriorly under local anesthesia and attaching low pressure suction is the generally recommended procedure. Serial chest films obtained with the portable x-ray apparatus will indicate the degree of re-expansion which has been achieved. The symptoms are usually relieved promptly by release of intrathoracic pressures. Suction drainage may be stopped 48 hours after full re-expansion, but may have to be reinstituted if collapse of the lung recurs.

At times adhesions in the apical region can be detected by roentgenogram, and may contribute to failure of re-expansion by closed drainage. Some surgeons have released these adhesions by thoracoscopic technique, whereas others have favored thoracotomy, at which time division of adhesions and closure of pleural leaks may be accomplished. At this time, most surgeons favor some means of assuring pleurodesis in the involved area. To this end, visceral pleurectomy, talc poudrage, abrasion of the visceral pleura with gauze or painting the pleura with 10 per cent silver nitrate have been performed. Recognition of the bleb may be very difficult since appreciable pneumothorax may result from an insignificant lesion. In longstanding cases, partial decortication of the lung may be necessary to assure re-expansion.

Thoracotomy may also be indicated when pneumothorax has recurred two or three times, although some surgeons have preferred a trial of talc poudrage or instillation of 10 per cent silver nitrate into the chest cavity by catheter in order to effect pleural

symphysis without thoracotomy. Should these conservative measures fail, thoracotomy is the procedure of choice

In some patients, empyema may develop as a complication of pneumothorax (as in Case F D) In some, this may be controlled by catheter drainage and periodic instillation of the proper antibiotic agent (as determined by culture and sensitivity studies) In others, the presence of fibrin or thick pus makes open drainage necessary, after the empyema has localized and the adjacent pleura has become adherent

Hemorrhage has been an uncommon complication of pneumothorax In such cases, aspiration and suction drainage may suffice if bleeding is minimal In a rare case, thoracotomy may be necessary to control blood loss from a torn adhesion or ruptured bleb

Emphysema in Infants and Children

In recent years there has been increasing surgical interest in what has been called "localized obstructive emphysema" or "lobar emphysema." Dyspnea, with or without cyanosis, occurs at an early age and may become severe within days after birth. Standard roentgenograms of the chest may at first suggest a diagnosis of simple pulmonary cysts, diaphragmatic hernia, agenesis of lung, atelectasis or pneumonia because of areas of varying density and mediastinal shift The process of overdistention of lung may develop rapidly, so that pneumothorax may be suspected if strands of pulmonary tissue are not recognized traversing the radiolucent spaces Although Eloesser, Head and others have considered these lesions to be overdistended congenital pulmonary cysts, infantile type, Dugan and Samson and others have included them with [illegible] in adults. Van

[illegible]

tion to differences in symptomatology, the respiratory distress being more severe with obstructive emphysema There were also distinguishing characteristics to the roentgenogram, in that "the vascular pattern in the emphysematous lobe is distorted and separated, and not as irregular and thin as the septa seen in cystic disease of the lung " The pathologic picture was different, as well.

In the emphysematous lung, there were focal atelectasis and dilated alveoli lined by flattened cells. There was no evidence of proliferation of embryonic lung tissue. In the case with cystic disease, the air spaces were lined with columnar epithelium.

Shaw has also described in detail the appearance of lung involved in diffuse lobar emphysema. "The diseased segment is enlarged to many times its normal volume in a uniform dilatation of the air sacs. The bronchi arteries and veins are much smaller than one would expect to find supplying a segment of lung. Even when the bronchi are opened and the segment of lung tissue is removed from the body, it does not collapse appreciably. It is uniformly pink in color even adults, indicating that it has not taken part in the usual ventilation of lung tissue. Except for the pink color, it more closely resembles Gelfoam than any other substance. Several hours after being removed from the body this tissue will float upon water with less than 1/10 of its volume being submerged. Microscopic examination of the tissue reveals air sacs and alveoli that are generally distended and empty. The intervening septae are thin and there is no inflammatory reaction. The blood vessels are small and have thin walls. The bronchioles are empty. The bronchial mucosa is normal except for slight chronic inflammatory infiltration. The cause of the emphysema is not evident in the examination of the specimens."

Caffey believes that there is a form of acquired emphysema ich can follow upper respiratory infections and which will re e in time. He does accept, however, the existence of a lobar ostructive emphysema developing probably on a congenital basis. This type does not respond to conservatism and demands surgical intervention in the presence of clinical symptoms. Infection does not occur commonly in this type and needle aspiration is most often unsuccessful in achieving satisfactory decompression. The involvement of an entire lung in an infant has been reported by Nelson and Brown. The patient had bronchostenosis and required pneumonectomy at the age of 7½ months. The reported causes in other ses have been weakness or deficiency of the bronchial cartilages nding to the affected lung, the presence of a redundant fold of eous membrane causing a valve like obstruction to the lobe.

and vascular anomalies in which extrinsic pressure was exerted on bronchi by aberrant vessels In many specimens, however, no convincing cause can be detected.

Also seen as surgical emergencies are rapidly enlarging congenital pulmonary cysts associated with obstructive emphysema Immediate operation and pulmonary resection is life saving, whereas conservatism most often has a fatal outcome

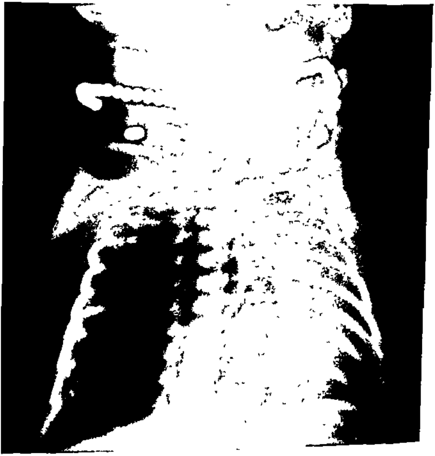

Fig 165

(A) Pre-operative emergency roengenogram of chest of four-day-old infant in the anteroposterior projection, revealing marked displacement of heart and mediastinum to the left with massive over distention of cysts in right lower lobe of lung

The following case is representative.

CASE J. H.

This three-day white male infant (#207696) was transferred from another hospital in extremis because of respiratory distress progressive from 24 hours of age. Cyanosis was noted with feedings from the second day and the child ate

FIG. 16.5 (cont.)

(...) Lateral film obtained at the same time reveals a small compressed upper middle lobe anterior to the cystic lower lobe.

poorly Examination revealed a distended right thorax with respiratory rate of 54 per minute; cyanosis occurred with crying; auscultation revealed no breath sounds on the right and percussion demonstrated hyper-resonance The liver edge was 2 cm. below the costal margin. Some edema was present in the scrotum Roentgenograms of the chest obtained prior to transfer revealed overdistended cystic areas in the right lung compressing uninvolved lung tissue anteriorly (fig. 16 5a and b)

On December 3, 1954, the right chest was entered through the fifth interspace The lower lobe of the lung was entirely replaced by tension cysts which bulged out of the wound Immediately there was an improvement in ventilation The lower lobe was resected allowing adequate expansion of the upper and middle

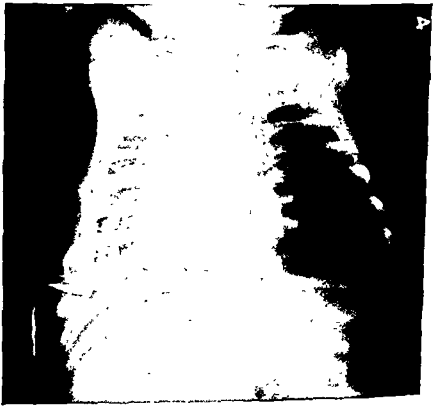

Fig 16 5 (*cont*)

(C) Roentgenogram of chest obtained one week after right lower lobe lobectomy and excision of cyst of lower esophagus An esophageal fistula has developed *but there is excellent re-expansion* of the right upper and middle lobes of the lung

lobes which appeared normal. In the region of the inferior pulmonary ligament there was noted cysts in the wall of the esophagus which were also excised, necessitating suture repair of the lateral wall of the esophagus. The stomach appeared to be completely undeveloped and nonrotated. A small tube was passed into the stomach for feeding. The patient's condition appeared very satisfactory although at six days there was evidence of an esophageal leakage (fig. 16.5c). Nutrition was adequately maintained through the tube although later a gastrostomy was performed. Ultimately the sinus tract to the chest wall closed but there was progressive narrowing of the area of the leakage (fig. 16.5d). Re-exploration through

Fig. 16.5 (cont.)

(D) Roentgenogram two months later reveals resolution of empyema and small angulated channel permitting passage of lipiodol into an infantile nonrotated stomach.

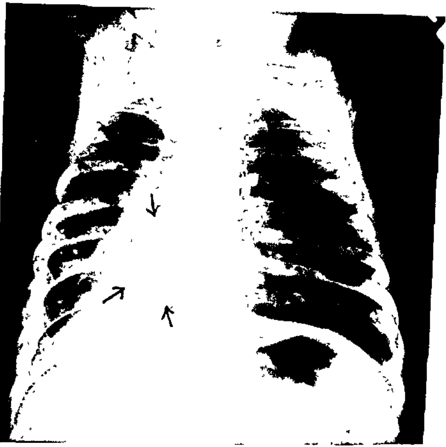

FIG 16 5 *(cont)*

(E) Chest film six months following right lower lobe lobectomy reveals slight pleural thickening about the diaphragm secondary to resolved empyema There is satisfactory expansion of the upper and middle lobes Arrows point to air in dilated esophagus proximal to the line of anastomosis

the left chest was necessary on May 17, 1955 At this time the esophagogastric junction was explored and adequate lumen achieved with re-anastomosis Subsequent to this recovery was uneventful and the patient has done well up the to last visit at age one year (fig 16 5e and f)

Microscopic sections of the right lower lobe revealed edematous lung tissue and large bleb-like areas beneath the pleural surface The entire lung was composed of these cystic spaces measuring up to 3 cm in diameter and lined with thin, glistening gray membrane Microscopic examination revealed hyperplasia

FIG 16 5 (cont)

(I) Esophagram in oblique projection reveals dilated esophagus just proximal to line of anastomosis with infantile nonrotated stomach

of cartilaginous plates, some of the cystic spaces were lined with cellular connective tissue where as others had a lining of tall columnar epithelium The esophageal cysts appeared to be reduplication cysts.

The first lobectomy for this condition was reported by Fischer, Tropea and Bailey, and additional cases have been reported subsequently by Gross and Lewis, Leahy and Butsch, Sweet, Lewis and Potts, Robertson and James, Shaw, Williams, Fischer, Potts and Holinger, Whitesell and White, Sloan, Ehrenhaft and Taber, DeBord and Sibilsky, and others The mortality rate with lung resection has been negligible. At time of surgery, the induction of anesthesia may be difficult but as soon as the thorax is opened, there is usually an immediate and dramatic improvement in ventilation This is what might be expected from the re-expansion of compressed or atelectatic lung tissue, concomitant with the release of the over-distended lung from the pleural space

Postoperatively, suction drainage is instituted for 36 to 72 hours to allow full re-expansion of residual pulmonary tissue In contrast to adults with generalized emphysema, the problems in management are minimal and the follow-up results are excellent.

Summary

Surgical therapy of diffuse hypertrophic emphysema has been discouraging Despite occasional patients who have been benefited by selective lung resection, autonomic nerve resection and other measures, this condition progresses and is generally subject to only mild and transient benefits from surgical methods

On the other hand, dramatic improvement has been noted following obliteration of large localized blebs or bullae which compressed adjacent junctional lung tissue As the multiplicity of blebs or bullae increase and as the amount of involvement of residual lung by diffuse emphysema increases, the expected benefits from surgical removal of these alveolar air cysts diminish In well advanced cases, improvement may be negligible or very transient

Results of conservative measures inciting pleural symphysis in patients with spontaneous pneumothorax may be satisfactory On the other hand, with chronic or recurrent pneumothorax, thora-

cotomy and definitive measures are generally indicated The results with such procedures are good Empyema or hemorrhage, complicating pneumothorax, may respond to conservative surgical therapy in some cases

A form of localized obstructive emphysema in children, at times associated with congenital cysts, may call for emergency resection of the involved lung as a life-saving procedure The follow-up results in these cases are much more encouraging than in patients with hypertrophic emphysema

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Chapter 17

RESPIRATORY FUNCTION TESTS

GEORGE R. MENEELY, M.D. AND JAMES J. CALLAWAY, M.D.

Introduction

Although pulmonary function testing seems a recent innovation, it is only widespread interest in it which is new. One recalls that Sir Humphry Davy estimated the residual volume of the lung by a foreign gas method (hydrogen) more than a hundred years ago and simultaneously observed the time course of the intrapulmonary mixing of gases as well. There are a number of reasons for the present upsurge of interest in the subject. In brief, wide use of roentgen diagnosis, the advent of practical tests of pulmonary function and commercial availability of equipment to perform them, the development of effective antibiotics and therapeutic products of synthetic chemistry, particularly bronchodilators, together with the conquest of the killing diseases of childhood and youth, and a consequent continually increasing proportion of middle and older aged in the population have all combined to increase the relative incidence and importance of the insidiously progressive chronic nonspecific pulmonary diseases of which pulmonary emphysema is the prime example. Our attention has therefore been compelled to impairment of pulmonary function, which, of course, has been with us to a degree immemorially but its presence was formerly obscured by more urgent and obvious matters. There is a great deal of difference between the theory of pulmonary physiology and the practical testing of pulmonary function. The research physiologist asks the question "Why?" and seeks the answer in hypothesis and experiment. The clinical laboratorian follows intently the investigations of his academic

colleague but the question he asks in his own demesne is: "*How much?*" and then, "Is that good or bad?" The pulmonary function tester must develop a scientific schizophrenia, must make one part of his mind crassly objective and confine his imagination to the other part where he admires and envies his investigative cousin There is a kind of physician who must examine the patient before he is willing to read a difficult electrocardiogram Nothing he finds at examination can possibly alter the deflections already inscribed on the recording but notions developed while seeing the patient can certainly bias him into projecting into the tracing things which simply are not there in reality It is a common complaint that reports of pulmonary function tests often contain more interpretation than information Bald facts are all that should emerge *from a clinical laboratory.* The physician will then want to attempt a reconciliation between these facts and others known *about the patient He should do so, but he is then practicing the* art of medicine and is no longer a laboratorian engaged in the *science of applied physiology*

For several years, The Section on Diseases of the Chest of The American Medical Association has sponsored an exhibit demonstrating the basic methods in practical pulmonary function testing intended to show what can be done in the doctors office and small clinical physiology laboratory. Much of that material is included here because it has proved to have broad appeal and is within the realm of the possible for this desirable end The physician whose particular practice makes him feel the need for quantitating the function of the lungs yet whose training does not provide him with the requisite know-how is the one to whom this chapter is addressed

Pulmonary function testing is an activity not a theory and, like any activity, it requires *a plan. One cannot engage in it* haphazardly to any profit and there is no "single test" of pulmonary function *The man who states "I can learn as much from looking at a* tracing of a single expiratory vital capacity as I can from a battery of tests" simply reveals a restricted variety or inadequate volume of experience Even at the hands of the most competent

there is no such thing as "complete pulmonary function tests," a phrase commonly abused in the profession

Broad competence in pulmonary function testing cannot be acquired by reading alone The original literature is enormous and difficult of access During the last two decades over 700 authors published articles which attracted at least enough attention to be quoted one or more times in other papers The leading articles were disseminated among 43 different medical journals without much concentration in any particular one of them There is no single authoritative source to which the reader may refer for all he needs to know even for the simplest activity, closed circuit respirometry A massive text, comparable to the venerable "Peters and Van Slyke" *in clinical chemistry is urgently needed but signs* of its coming are not yet Rather than a detailed documentation of the field, the references cited suffice only to lead the reader into the field and, perhaps, in themselves embody a larger than average scholarship of the subject

Planning a Pulmonary Function Testing Program

There is as much need in the modern hospital for a lung station as there is for a heart station and one can be staffed and equipped at no greater expense than the other A clear definition of objectives is essential Consideration must be given to what tests of function can and cannot do and the real professional, technical, physical, and financial resources available

The common denominator among patients referred for pulmonary function testing is that they have or are suspected of having chronic pulmonary disease The general purpose of pulmonary function testing is to detect impairment and, if present, to characterize it and estimate its severity The specific purpose derives from the nature of the problem which the particular patient presents to his doctors *or to interested third parties such as insurance* companies, employers or compensation boards A routine suitable for one purpose may not serve another, although certain tests should probably be employed in every case

There is often a lack of awareness that some of the outstanding

laboratories, from which emanate a large fraction of the important publications in the field, are primarily research organizations which, despite a large staff, a heavy investment in equipment and a generous operating budget actually work up only a few patients each week In a laboratory organized to provide a clinical service, close attention must be given to the versatility of each instrument, the level of technical skill required to operate it, and the amount of time involved in each test. In the long run, personnel becomes the major budgetary item and efficiency is at a premium Often a larger investment in equipment is justified by the rapidity or facility with which individual tests can be performed

The traditional approach to the problem of pulmonary function testing is to develop a schema of the respiratory processes and then review methods available for testing each component However desirable this may be for teaching purposes, it does not answer the practical question Laboratory activities are circumscribed by instrumental resources and the skill and available time of the medical and technical staff Tests of pulmonary function can be classified horizontally by purpose and vertically by degree of complexity, equipment required and extent of experience needed to perform them It is logical, therefore, to approach the problem by reviewing the instruments which have been found generally useful and analyzing what can be accomplished with them. Then, with the particular objectives clearly outlined, it should be possible to select the equipment which most nearly fits the requirement, set up the desired methods and operate an effective lung station within the framework of the available real resources

Three important collateral matters must be considered First, fluoroscopy is of such importance in all aspects of chronic pulmonary disease that it must be assumed a fluoroscope is available and that the doctor responsible for function testing personally fluoroscopes each patient as an integral part of the routine. Second, close integration of the clinical cardiac and respiratory laboratory program is always desirable and particularly so if advanced procedures are to be employed, because there is a large overlap of methodology Efficient and economical utilization of skilled

personnel and elaborate equipment dictates adjacent physical location or even actual combination if wasteful duplication of equipment and technical skills is to be avoided There are, of course, circumstances which may require separate establishments but in any event, cooperation and close integration are invaluable Third, the training and experience of the doctor responsible for the testing program may justify selection of particular methods because of personal familiarity with them and confidence in them

There is now fairly general agreement on "basic" equipment and methods The irreducible minimum procedure which can be termed a test of pulmonary function is the determination of timed vital capacity, *i e*, one-second, three-second and total vital capacity and total vital capacity time Relatively simple equipment suffices and the procedure is suitable for office work as well as in the small hospital or clinic Closed circuit respirometry with a well-constructed low resistance two-speed recording respirometer with ventilograph is certainly the next step This versatile instrument is also practical for office use by men particularly interested in chest disease Next in order is determination of arterial oxygen saturation and CO_2 content The basic method today employs the Cournand needle, syringe sample storage and analysis with the manometric Van Slyke apparatus Other methods are promising, but are not recommended for routine use at the present time

When this much has been made available, it is highly desirable to add arterial pH determination with a modern, simple, direct, glass electrode blood pH meter Next, determination of the lung volume and its fractions is widely accepted as the best measure of the degree of pulmonary distention present and of special value in the appraisal of pulmonary emphysema, but agreement is less general about methodology All of the methods in current use give values which are useful clinically Whether bronchospirometry is included in the "basic" repertoire will depend upon the specific purpose of the program and is most generally useful in pre- and postoperative evaluation of thoracic surgery patients

There are a large number of procedures which are "on the way" from the research laboratory to the clinic The extent to which the

basic repertoire may be expanded is limitless, but contemplated additions should be considered carefully in terms of their established value and the instrument and time investment required.

Comroe has ably summarized what pulmonary function tests can and cannot do They can provide the information needed for an objective appraisal of pulmonary impairment, insufficiency or disability when interpreted in relation to the other findings in the patient Extensive involvement of the lungs seen in x-ray shadows may be associated with little or no pulmonary impairment, and others with little roentgenologic evidence of disease may have true pulmonary disability They may be useful in ruling out pulmonary disease in nonorganic types of dyspnea such as psychoneurosis, neurocirculatory asthenia, etc They may provide a quantitative measure of pulmonary function which can aid in the evaluation of candidates for permanent forms of collapse therapy or surgical removal of lung tissue, both so far as immediate risk and ultimate useful existence are concerned They may aid in following objectively certain aspects of the course of pulmonary disease or permit evaluation of therapeutic measures, medical or surgical Help in differentiating cardiac from pulmonary disease and in differentiating primary from secondary types of polycythemia may be obtained Occasionally, they permit detection of pulmonary abnormalities in patients in whom physical examination and x-ray studies cannot disclose certain diseases of the lung In pre-employment evaluation in certain occupations they may be useful In evaluating disability claims in insurance or industrial practice they are of major importance Pulmonary function studies indicate the specific function of the lung that has been impaired and give the physician a clearer concept of the disease process in each patient

Pulmonary function tests cannot be expected to provide etiologic or anatomic diagnoses but only physiologic diagnoses, estimates of functional capacity and, sometimes, information of prognostic import They cannot localize a process geographically: thus certain tests might reveal the existence of a venous-arterial shunt but in themselves fail to identify it as intracardiac or intrapulmonic, nor can they distinguish between processes producing

certain effects, for example, impaired diffusion across the alveolo-capillary membrane might be demonstrated but without distinguishing between alveolar edema and interstitial edema. They cannot reveal pulmonary disease unless function is impaired and then only when impairment is of sufficient degree that present tests can recognize with certainty the deviation from normal values, thus slight reduction in function cannot be detected nor involvement of small areas only. Localized disease produces changes only when so much space is occupied or the lesion is strategically situated so that function is affected. As with other parenchymatous organs, diffuse disease is far more likely to impair function than localized lesions. They cannot supplant careful analysis of the history, physical examination, fluoroscopic and other radiologic examinations, bacteriologic or pathologic studies. At present sufficient data have not been obtained upon large enough groups of healthy persons to determine with certainty what constitutes normal values for pulmonary function in men and women of all age groups and what values represent an irreducible minimum below which patients cannot live in comfort.

Definitions

Definitions are the bane of pulmonary function testing because there is a multiplicity of them, each in some great or small way different, but it is necessary to define what is to be tested before any test can have meaning. A quarter of a century ago Christie complained of the many terms then in use for the volume of the lungs and its subdivisions, and the matter grew worse thereafter. In April of 1950 a committee chairmanned by Pappenheimer met in Atlantic City to establish a systematic set of definitions and symbols for use in teaching. Unfortunately, many of the measures which have become routine in clinical pulmonary function testing are either impossible of expression by this notation or when so expressed are needlessly cumbersome or abstruse. Another defect in the notation is that it cannot be used on an ordinary typewriter. It is entirely unnecessary, indeed undesirable, for simple clinical purposes to try to use this symbolic notation primarily designed for advanced students of respiratory physiology for all expressions

of information Most workers in the clinical laboratory field adhere to the Pappenheimer Committee Definitions of the lung volume and its subdivisions and use the rest of it when possible or practical When appropriate it is used in this chapter.

Respiration embraces the entire process of gaseous exchange between an organism and its environment *Internal respiration* is the exchange of gases between tissue cells and the fluid bathing these cells *External respiration* is the exchange of gases between the blood and the air entering the lung. External respiration is the subject of clinical pulmonary function testing

There are four basic mechanisms involved in external respiration *Ventilation* concerns the movement of air in and out of the lung *Mixing* is the intrapulmonary mixing of the respiratory gases *Diffusion* refers to the exchange of oxygen and carbon dioxide across the alveolocapillary membrane. *Perfusion* (or *circulation*) concerns the quantity and distribution of blood flow through the lungs It is convenient to think of tests of pulmonary function as evaluating elements of or combinations of these four mechanisms The diffusion-perfusion combination may be tested by relatively simple methods If a defect is present, however, definitive separation of these two is possible only by complex and elaborate methods beyond the resources of all but advanced laboratories

Impairment, insufficiency and *disability* are frequently misused terms It is important that the specific meaning of each of these words be recognized and that each be used correctly. *Impairment*: a specific function or group of functions is impaired if it deviates significantly from established normal standards. *Insufficiency:* a specific function is insufficient if it fails to meet normal requirements for ordinary activity *or* requires abnormal compensatory efforts to meet normal requirements *Disability:* the individual is rendered incapable of meeting the requirements of ordinary activity. It may thus be seen that *impairment* pertains to the function itself as compared to a normal standard *Insufficiency* pertains to effects produced in the organism by deprivation of a needed function and *disability* pertains to the effects of insuffi-

ciency upon the ability of the individual to meet the day-to-day demands imposed by ordinary activity.

It is essential in comparison of observations to normal standards to know the conditions under which the tests were performed Specifically, one must know the status of the patient, whether the tests were done while he was rested and quiet, during an asthmatic attack, etc It is usually sufficient for pulmonary function tests that the patient rest for a half hour or so, it is not necessary to delay meals although obviously one would not wish to test a patient too soon after a heavy meal The patient's age, sex, height and weight are required data The position of the patient must also be known—supine, sitting, reclining, etc

Observations of volumes must be corrected to some standard condition Those commonly used are. *Standard conditions of temperature and pressure, dry* (STPD) which is appropriate when chemical calculations are to be made, for example, of oxygen consumption or carbon dioxide excretion, *Normal body temperature, ambient barometric pressure, saturated with water vapor* (BTPS) which is used in calculation of volumes of body compartments such as the lung volume and its subdivisions because here one wishes to know the volume of the compartment, not what would be the volume of the gas it contains at some other temperature or pressure, *Ambient temperature and barometric pressure, saturated with water vapor* (ATPS) which is appropriate to express volumes of gas moved by the breathing action of the lung, because here it is important to know the effective action of the pumping system on the ambient air, not what volume changes occur in the gas pumped during the brief time of passage through the lung Given the observations, the physician interpreting them will need to refer to normal standards It is outside the scope of this chapter to tabulate the variety of standards currently in use, but ample references to sources for them are provided in the bibliography As time goes on, new and better standards are continually being developed Each laboratory will eventually settle upon its own choice with its own modifications made as it becomes evident such are needed It is unfortunately true that most normal standards are based

upon a paucity of data but slowly this defect is being remedied. Especially sparse are data for women, children and older men. Each interested physician must settle for himself the question of how much impairment of function represents a "normal" age change, how much is due to long-standing "chronic bronchitis" and how this relates to the problem of disability, especially if compensation is a question. Observations may be related to normal standards in several ways. Tables, graphs or equations based upon height, weight, age, sex or relations among observations in normal subjects may be used to obtain a *predicted* value which is the most probable value for the particular observation for a normal subject under similar circumstances. The value obtained from the patient may then be expressed as a per cent of the predicted value (*% pred*) or the difference between the observed value and the predicted value may be expressed as a per cent of the predicted value (*% dif*).

Figure 17.1 shows the volume of the lung and its subdivisions with the nomenclature settled upon by the Pappenheimer Committee. The term lung volume has been complained of by editors as consisting of two nouns. However, as one author pointed out, if one were determined to use the adjectival forms, making horse serum equine serum, one might, with similar material from another source be compelled to call it asinine serum. All volumes are

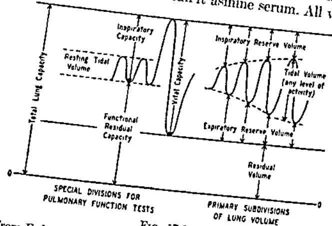


FIG. 17.1
(From Fed. Proc., 9: 602, 1950. Pappenheimer Committee report.)

corrected to BTPS for reasons explained above. The *tidal volume* (TV) is the average volume of each breath, the *expiratory reserve volume* (ERV) is that volume which can be expelled by a maximal expiratory effort beginning at the end of a normal expiration and the *residual volume* (RV) is the volume of gas remaining in the lung at the end of a maximal expiration. The "capacity" fractions consist of two or more of the single "volume" fractions. *Inspiratory capacity* (IC) is the volume inspired by maximal inspiratory effort beginning at the end of a normal expiration (the sum of tidal volume and inspiratory reserve volume). The *vital capacity* (VC) may be defined two ways, either as the sum of expiratory reserve volume and inspiratory capacity determined separately (two stage VC) or as that volume which can be expelled by a maximal expiratory effort after a maximal inspiratory effort (one stage VC). The *functional residual capacity* (FRC) is the volume of air remaining in the lung at the end of normal expiration, being the sum of expiratory reserve volume and residual volume. The *total lung capacity* (TC) is the volume of the lung at maximal inspiration and consists of the sum of vital capacity and residual volume. The volume of the lung and its subdivisions differs with position as well as age, sex, height and weight. It is probably best to measure it with the patient semirecumbent since this is a position which can be tolerated by all but the most orthopneic cardiac patients.

Definitions relating to ventilation studies are cumbersome when expressed in the Pappenheimer Committee notation and in this chapter the clinical terms in common use are given. *Minute ventilation* (MV) is the volume of air moved by the lung per minute under any condition with the patient in any position, but the condition must be specified. It is customary (but incorrect) to use the term for resting minute ventilation. Ordinarily it is measured in the same position and with the same equipment used for other ventilation studies so it may be comparable. This is a point where differences of opinion exist among applied physiologists. If the volume of the lung is to be measured by the closed circuit helium method, which seems to be the most rapid and efficient procedure for routine clinical use, resting minute ventilation in the semi-

recumbent position is obtainable from the tracings as well as the two stage vital capacity and its fractions The other tests of ventilation routinely used (see below) are usually performed with the *patient standing if he is able*, or at least sitting upright. In some laboratories these latter tests are done with a different apparatus The question then arises whether resting ventilation and the vital capacity and its fractions should again be determined under the new conditions Some feel that comparisons made between semi-recumbent resting minute ventilation and other measurements with the patient erect is like subtracting oranges from apples. The physician charged with routine pulmonary function testing will have to decide for himself whether the differences observed are worth the added technician (or his own) time. *Maximal minute ventilation* (MMV) sometimes called *maximum breathing capacity* (MBC) is that volume of air (expressed in liters per minute) which can be moved by bellows action of the lung during a brief period (usually 12 to 15 seconds) of maximal voluntary hyperventilation The *breathing reserve* (BR) sometimes called *ventilatory reserve* (VR) is the maximum breathing capacity minus the resting minute ventilation It is not an especially useful datum in itself, being that part of the maximal possible ventilation rate which the patient does not use at rest, but it is useful when expressed as the ratio (per cent) of breathing reserve to maximum breathing capacity (BR/MBC × 100) The *oxygen removal ratio* (ORR) (sometimes and unfortunately called the utilization coefficient which has another and quite different meaning) is the number of milli-

body but the variation among normals is so large (±27 per cent according to Hurtado and Boller) that it proves of little use in evaluation of impaired pulmonary function The reason for this apparent paradox is that ventilation is controlled from moment to moment mainly in the interest of holding the pH concentration of the blood within narrow limits by maintaining suitable levels of alveolar CO_2 tension Oxygen tension of blood plays a major role in maintaining ventilation only among patients with extreme

degrees of pulmonary insufficiency in whom CO_2 retention is excessive and the primary centers of ventilatory control have become insensitive to it. The term *ventilatory equivalent* (VE) has a reciprocal relation to ORR, being the number of liters ventilated per 100 ml. of oxygen consumed (VE = 100/ORR). The *air velocity index* (AVI) is the observed maximum breathing capacity expressed as a per cent of the predicted value divided by the vital capacity expressed as a per cent of the predicted value. A distaste for conventional mathematical terminology occasionally leads physicians down strange semantic garden pathways. The *mid-half vital capacity liter time* in seconds per liter is the average time in seconds required to expel a liter of air during the middle one-half of the one stage vital capacity determination. The concept is that measurements during the early part (specifically the first one-quarter of the total vital capacity) are marred by difficulty in determining the exact time of beginning expiration and measurements during the latter part (specifically the last one-quarter) are of dubious value because the patient is straining to do something not ordinarily done; consequently the middle one-half of the curve should be the best information upon which to base an appraisal of the rapidity with which he can move air. The *index of intrapulmonary mixing* (IIM) is the per cent concentration of nitrogen in a Haldane-Priestly sample of alveolar air obtained after seven minutes of 100 per cent oxygen breathing in the open circuit method of measuring functioning residual air. An essentially comparable figure is the half-time to reach equilibrium concentration in other methods of measuring FRC.

With regard to blood gases, in pulmonary function testing primary concern is with the gases of arterial blood. For most purposes, venous samples are not meaningful unless mixed venous blood is obtained with a cardiac catheter from the pulmonary artery or, less desirably, the right ventricle. *Arterial oxygen content* is the concentration of oxygen in arterial blood in milliliters per one hundred milliliters of blood (Vol. %). *Arterial carbon dioxide content* is the concentration of carbon dioxide in arterial blood. *Arterial oxygen capacity* is the maximum amount of oxygen which can combine with a sample of arterial blood. *Arterial oxy-*

gen saturation is the arterial oxygen content expressed as a per cent of the arterial oxygen capacity.

Arterial pH is the hydrogen ion concentration of arterial blood expressed in pH units (*the negative logarithm of the hydrogen ion concentration*) Only recently have glass electrodes suitable for direct pH determinations in arterial blood become available For the most part this measurement has been made in research laboratories only It is hoped that it will become more widely available because, when the CO_2 content of arterial blood is available also, much can be learned about the adequacy of the patient's ventilation This is discussed at greater length below

When one is concerned with gases in solution in body fluids it is necessary to understand the term *partial pressure*. At equilibrium, gases in solution exert a pressure exactly as do gases in the air in the sense that differences in pressure between gases in solution and gases in the air over the liquid results in gas molecules moving from the liquid to the gas or vice versa as the relative pressure in one or the other is higher Of the pressure exerted by the atmosphere (barometric pressure) part is exerted by oxygen, part by CO_2, part by water vapor and part by the physiologically inert gases, mainly nitrogen Each gas exerts a part of the total barometric pressure exactly proportional to its concentration in the gas phase, and if a liquid is in equilibrium with that gas, the partial pressures exerted by the physically dissolved gases will be exactly the same in the liquid as in the gas phase. Within the body at normal body temperature water vapor always exerts a partial pressure equal to 47 mm of mercury. The partial pressure of any other gas whether in the lung as gas or physically dissolved in blood may be calculated by deducting 47 mm. Hg from ambient barometric pressure and multiplying the difference by the per cent concentration of the gas divided by 100 The partial pressure of CO_2 in blood is the primary factor in changes of the pH concentration from moment to moment *Since the CO_2 of arterial blood* is virtually always in equilibrium with average alveolar partial pressure of CO_2, *the latter is manifestly of great importance* It in turn is determined by the adequacy of ventilation and, conse-

quently, determination of arterial (or average alveolar) CO_2 partial pressure is of great value in evaluating pulmonary function Methods to determine this statistic routinely are rapidly improving and soon should be widely available Since at present they are not, further discussion here would be profitless

EQUIPMENT

Some general comments regarding equipment have already been made in the introduction to this chapter Elsewhere in this volume more elaborate procedures are mentioned Here it is intended to outline simple procedures which can be established for routine use in the doctor's office, the small hospital or the clinic Most of the tests can be performed by a technician alone The physician in charge can review the data and tracings obtained at the end of the day, determining then which patients need more elaborate study Arterial puncture for samples of arterial blood must, of course, be done by a physician but the blood gas analysis may then be done by a technician Glass electrode pH meters should be used only by especially skilled individuals, which should most probably mean the physician concerned, especially since the determination should be made immediately rather than in stored samples The procedure is different for each apparatus, and, since this certainly classifies as an "advanced method" further details on the subject will not be given in this chapter

An apparatus for timed vital capacity determinations such as diagrammed in Figure 17 2 is the irreducible minimum equipment for any testing of pulmonary function It is a valuable adjunct in the doctor's office, being useful in cardiac patients also and in the hospital or clinic with a pulmonary function testing laboratory it serves useful purposes too It may be made available to the house staff, can readily be moved from place to place, is not especially fragile nor extremely expensive and serves to spread the gospel of the usefulness of pulmonary function tests In some centers it is required that timed vital capacity measurements be made on the ward or in the clinic before patients are referred to the laboratory for more complete testing It is certainly of value as a screening

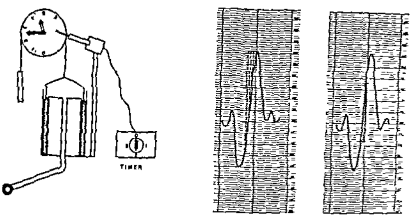


FIG. 17 2 Timing of the vital capacity

Measuring the speed of performance of the VC is as important as the measure of the volume of the total VC It is one of the simplest methods for differentiating obstructive and restrictive ventilatory insufficiency. There are many methods for introducing the element of time into the vital capacity measurement

"Timed Vitalometer" An electronic timer (with selection for the desired time interval) actuates a solenoid which stops the recording of the VC at a predetermined time interval

Timed VC Measured with a Recording Spirometer: The desired time intervals are measured on the record of the vital capacity effort.

Mid-Half VC Time: Whereas the other two methods measure the volume of the VC exhaled in a given time, the mid-half VC time measures the time required for exhaling the middle half of the vital capacity.

test A patient with perfectly normal values in timed vital capacity procedure is not likely to manifest much impairment in other tests of ventilatory function

Beyond an instrument for timed vital capacity, a recording respirometer with ventilograph attachment designed for pulmonary function testing is certainly the next step A considerable variety of studies may be done with it. For the doctor's office it may be recalled that the apparatus can also be used for basal metabolic rate determinations although BMR equipment is *not* suitable for respirometry The kymograph should run at two

speeds (½ mm/sec and 2½ mm/sec) The ventilograph pen totalizes the excursions of the pen recording the respiratory tracing at a fixed ratio of 1:10 yielding a tracing from which ventilatory rates may be read directly Spirograms in normals from day to day and week to week are uniform for the individual although they vary from person to person As recorded data they may be compared with future spirograms and progress and changes in the patient's condition more easily evaulated With the CO_2 absorber (soda-lime container) in place, oxygen consumption may be measured from the slope of the baseline The term respiratory baseline refers to a line drawn through the average position of the points on the tracing marking the end of expiration The tracings help in evaluating the patient's cooperative effort and his general breathing pattern Hyperventilation may be noted or irregular breathing patterns, sighing respiration, wandering baseline and the like. Slow paper speed is appropriate for oxygen consumption measurements but the fast paper speed should be used to study the patterns as well as for vital capacity measurements with the soda-lime canister removed It is well to measure single stage vital capacity tracings beginning at maximal inspiration and beginning at maximal expiration The two should be equal The one-, two- and three-second vital capacity, the total vital capacity, the total vital capacity time may all readily be measured from the tracings (Fig 17 2) A Segal-Herschfus ruler is helpful for the purpose The time-volume relationships of the middle one-half of the vital capacity may also readily be measured from the tracings Fractions of the lung volume should always be corrected to BTPS as earlier stated, and ventilation figures should be given at ATPS Diminished one-second vital capacity is an indication of obstruction and of loss of pulmonary elasticity The three-second vital capacity is the maximum useable portion of the vital capacity In obstruction, bronchoconstriction may be tested for by use of adrenalin or other effective bronchodilators Tracings after bronchodilator may show improvement in the one- and three-second vital capacity and shortening of the total vital capacity time

Trapping is best demonstrated by three successive one-stage determinations of vital capacity If trapping is important, the

excursions become progressively smaller. If this is due to obstruction which can be relieved, adrenalin will change the pattern toward normal

Two-stage vital capacity, in which inspiratory capacity and expiratory reserve volume are determined separately and added, normally equals the one-stage vital capacity In emphysema two-stage vital capacity is significantly larger. Adrenalin or other efficient bronchodilators may increase inspiratory capacity and reduce expiratory reserve volume if reversible obstruction is present

Maximum breathing capacity is usually performed with the patient erect There is some debate about the size of spirometer most desirable for MBC Some feel that a very large respirometer (13 5 liter bell) should be used The cost is higher and the instrument physically is more cumbersome than the standard respirometer (9 liter) There is less resistance in the large instrument, especially if small Sadd valves in the smaller instrument are compared with diaphragm type high velocity valves in the larger If all valves are removed, the difference is less and if a blower is used with the 9-liter instrument, the smaller may be better There is much more to the problem than diameter and angulation of the air passages of the instrument, however Each spirometer bell and counter-weight system has a certain inertia as well as a certain natural frequency of oscillation In general, the greater the inertia of the system, the less faithfully it will follow applied forces Away from the natural frequency of the system, inertia results in bell-counterweight excursions which are too small but as the natural frequency of oscillation is approached by the respiratory rate, resonance develops and the excursions of the bell-counterweight system exceed in magnitude the impressed changes Various groups are engaged in attempts to improve spirometers in this regard but perhaps it should be pointed out, in view of the physical principals involved, that a bell pulley-counterweight-pen-paper system is inherently bad for the purpose of recording rapid reciprocating fluctuations in gas flow rates If one wishes to attain higher levels of precision work along some other line such as research with a pneumotachygraph would probably be more rewarding than elaborate redesigning and refinement of an existing

apparatus which on the whole is fairly satisfactory for the purpose for which it was intended, routine clinical respirometry.

It is perhaps in the routine determination of maximum minute ventilation that the superiority of modern closed circuit methods over open circuit methods is most clearly apparent. The Douglas bag, the Tissot spirometer and the stop watch are venerable tools in a venerable trade but a recorded tracing of maximum minute ventilation is not only more readily accomplished but it contains information not obtainable with the open method. In the latter case nothing may be learned of the respiratory baseline changes. Normally the maximum minute ventilation is performed both above and below the baseline of the resting pattern but obstruction and loss of pulmonary elasticity cause it to be performed above the resting level as the patient attempts to overcome obstruction and make use of what elasticity remains. If obstruction is reversible, as seen strikingly in asthma, adrenalin will relieve it, increasing the maximum minute ventilation and lowering the baseline at which it is performed. The rate and tidal volume have an interesting relationship in maximum minute ventilation. Unfortunately, good normal standards for reference do not exist, but it is worthwhile to note the rate of respiration and the average tidal volume during maximum minute ventilation because it is characteristic of all forms of pulmonary impairment that increase of respiratory rate is greater and increase of tidal volume less than in normals. The air contained in the respiratory passages, a volume of approximately 125 ml., is of no use in alveolocapillary gas exchange but must be inhaled and exhaled again with each breath. When tidal volume is large, it is a small fraction of it, but when tidal volume is small, it may represent a large fraction and so greatly diminish alveolar ventilation. It is well known that shallow panting is highly inefficient respiration, the ventilation of the trained athlete during steady exertion is characterized by very large tidal volumes at a relatively slow rate.

It is in the measurement of maximum minute ventilation that the ability of the pulmonary function technician comes most clearly into test. A high degree of an almost religious fervor is an essential to adequate performance. The patient must be exhorted

to do his best and vigorous gestures and yelps of encouragement should cheer him on through the 12 to 15 seconds of his maximal voluntary hyperventilation. A really capable and personable female technician can inspire even a malingerer to surprising levels of gas exchange

It is curious that the voluntary hyperventilation method introduced by Hermannsen should prove such a reproducible procedure. One would suppose that motivation, momentary emotional state or fluctuations in the day to day level of general well-being would introduce high variation in such a procedure but this is not the case The method has been repeatedly shown to be superior to others tried such as CO_2 breathing or ventilation observed during exercise

A word about exercise in relation to pulmonary function is in order *Ventilation is controlled by four different elements: Arterial* partial pressure of CO_2, blood pH, partial pressure of oxygen and *the "muscular exertion factor." Gray has formulated the interrelation of these in the multiple factor theory of the control of ventilation. The extent to which muscular exertion, independent* of changes in pH, pCO_2 and pO_2, influences ventilation is large *and highly variable, being dependent upon a variety of factors* but most especially the general physical fitness of the patient and having little or nothing to do with the condition of the lungs. Consequently, this large variable in the control of ventilation during exercise makes observations of ventilation with exercise almost entirely useless in evaluating pulmonary function as such Exercise studies are of the utmost importance if one is concerned with evaluating the general fitness of a patient, but in routine pulmonary function testing exercise is useful only to increase metabolic demand in order to determine whether the lungs can maintain or increase arterial oxygen saturation as normally they can. It is possible by rather elaborate studies to characterize fairly well the cardiorespiratory response during a carefully measured bout of exercise and the period following it, but simple observations of ventilation are utterly inadequate for the purpose and the full-dress study with determinations of oxygen consumption, CO_2 excretion, respiratory quotient changes, oxygen debt estimation and

calculations of mechanical efficiency go far beyond the requisites of routine clinical pulmonary function testing The confidence which some repose in observations of the ability of patients to tolerate exercise simply reflects the great importance of general physical fitness of the patient who is perhaps to be subjected to major surgery Again, when ventilation during exercise is compared among categories of patients with different varieties of pulmonary disease with ventilatory impairment, significant differences between mean values are frequently found This contributes to our understanding of the general physiologic principles involved in the different general effects of the particular disorders However, when the considerable volume of published data on this score is analyzed statistically it is immediately apparent variance in the different categories is so large that useful diagnostic probabilities for the individual patient cannot be derived Similarly, although Irishmen average a little taller than Englishmen, no useful probability about whether a man is Irish or English can be based on his observed height

The characteristic alteration of timed vital capacity in restrictive ventilatory insufficiency is illustrated in Figure 17 3 There may be marked diminution in absolute volumes with only moderate diminution in the velocity with which air is moved In contrast, in obstructive ventilatory insufficiency the diminution in *absolute volumes* may be large and the velocity with which the respiratory gases can be moved is greatly reduced as well (Fig 17 4) The importance of the time relations of the vital capacity *has been recognized for long* in Europe, especially in the French literature, but the popularization of timed vital capacity as a test of pulmonary function in America is due largely to Gaensler who devised *the simple electronic* timer now widely used He investigated a variety of patients with altered pulmonary function This data is summarized in Figures 17 5 and 17 6 It is important to note that there *are differences of opinion* about the vital capacity in pregnancy Gaensler's data suggest a slight diminution in total vital capacity The extensive studies of the Boston group on the physiology of pregnancy *and particularly studies relating* to heart disease complicated by pregnancy have emphasized the usefulness

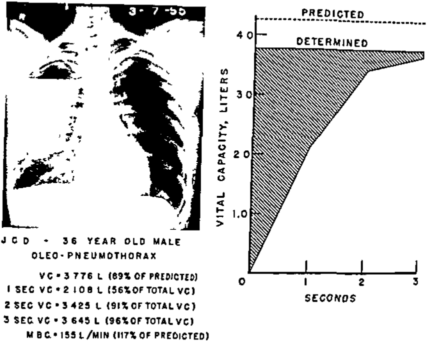


Fig 17 3 Restrictive ventilatory insufficiency

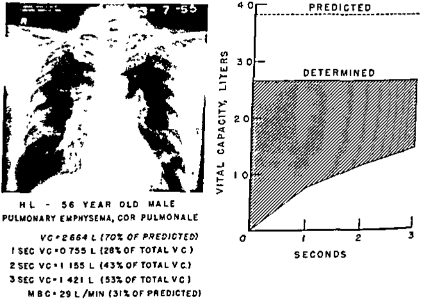


Fig 17 4 Obstructive ventilatory insufficiency

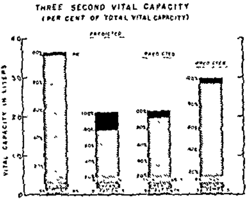


FIG. 17.5 Restrictive ventilatory insufficiency (From E. A. Gaensler, Am Rev. Tuberc., 64: 257-278, 1951.)

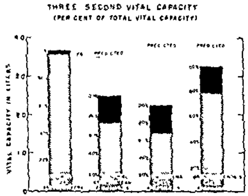


FIG. 17.6 Obstructive ventilatory insufficiency (From E. A. Gaensler, Am Rev. Tuberc., 64: 257-278, 1951.)

of total vital capacity measurements in pregnant cardiac patients. Since the total vital capacity *does not substantially* diminish in the course of pregnancy in women without heart disease and may even increase, the detection of progressively diminishing vital *capacity in pregnant cardiac* patients is a reliable sign of developing congestive failure.

Closed circuit respirometry with a well-made low resistance two-

speed recording instrument is one of the simplest, most direct, easily understood, and, at the same time, one of the most valuable *procedures in routine pulmonary function testing* The Warren Collins instrument, in essence a modified and greatly improved version of the Benedict-Roth basal metabolism apparatus, exemplifies the important contribution manufacturers of scientific instruments make to advances in medicine. Engineering development and commercial production of equipment which can be unpacked, set up and put to immediate use is necessary to bring a clinical physiologic method out of the research laboratory. Availability of the Collins instrument has been an important factor in the recent rapid growth of routine pulmonary function testing Those who recall the tedious measuring of ventilation from the respiratory tracing are especially grateful for the ventilograph originated by Reichert which writes a tracing proportional to the sum of the inspiratory excursions. This gives ventilation directly (Fig 17 7)

Examples of observations made by closed circuit respirometry in three patients with restrictive ventilatory insufficiency are shown *in Figures 17 8, 17 9 and 17.10. These were made for demonstration* purposes It is neither necessary nor desirable to try to compress the testing into such a short tracing Spirographic studies characteristically reveal loss of total lung volume with decreased vital capacity There usually is no slowing in the expiratory vital capacity as seen when the time relations are measured Maximum minute ventilation may not be reduced If it is, the reduction is disproportionately *less than in vital capacity*. The respiratory baseline rises little if at all during maximal ventilatory effort

Obstructive ventilatory insufficiency refers to the sort usually seen in pulmonary emphysema The words *restrictive* and *obstructive*, to characterize the two basic forms of alteration of ventilation in disease, are in effect abbreviations and suffer from the semantic difficulties inherent *in summarizing complex concepts in a single* word Older custom used the terms fibrotic and emphysematous to characterize the two types The term fibrotic is misleading because many things may restrict the bellows action of the lung

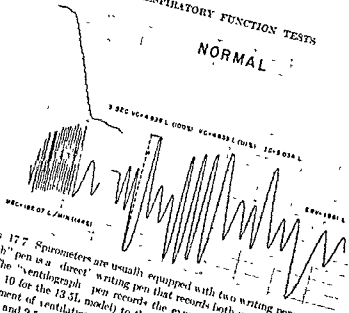


FIG 17 7 Spirometers are usually equipped with two writing pens The "spirograph" pen is a 'direct' writing pen that records both inspiration and expiration The "ventilograph" pen records the expiratory volumes only in a fixed ratio (1 10 for the 13 5L model) to the spirograph pen This greatly facilitates measurement of ventilation volumes The Kymograph runs at two speeds 0 5 mm /sec and 2 5 mm /sec

Vital Capacity Recorded at 2 5 mm sec for accuracy of measurement The form of the inspiratory and expiratory curves can be seen readily Total VC time and timed VCs can be measured *Two Stage Vital Capacity* Obtained by adding the separate values for IC and ERV *Air Trapping* Best demonstrated by successive determinations of the VC If the VC becomes progressively smaller trapping is present

Maximum Breathing Capacity Recorded at 2 5 mm sec The ventilation volume is measured from the "ventilograph" tracing The normal MBC is performed below and above the baseline for tidal volume

The accompanying spirograms were recorded on a Collins 13 5L Spirometer

without any demonstrable fibrosis The term *restrictive ventilatory defect* is more rational than the older word There is more question whether 'obstructive ventilatory defect" is an improvement To the pulmonary physiologist, emphysema is chronic pulmonary distention Acute pulmonary distention may occur, for example during an attack of asthma, due entirely to obstruction, especially of expiration Obstruction may be an important element in chronic pulmonary distention demonstrably so when reversible but re-

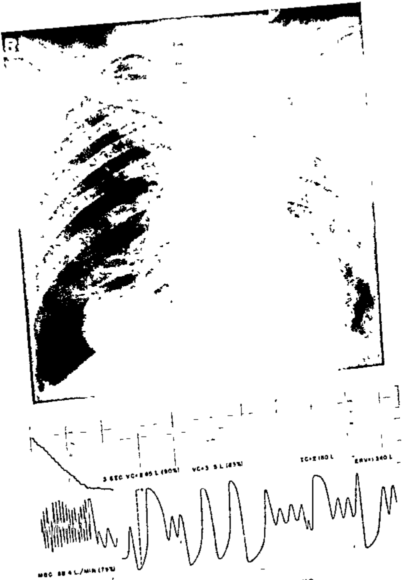


FIG 17 8. Bronchogenic carcinoma

C. C 58-year-old male *Chief complaint* Cough, weakness and 20 pound weight loss for 5 months *Additional pulmonary function data* RV/TLC × 100 8%, S_{aO_2} 94 7%; C_{aCO_2} 52 5 vol %

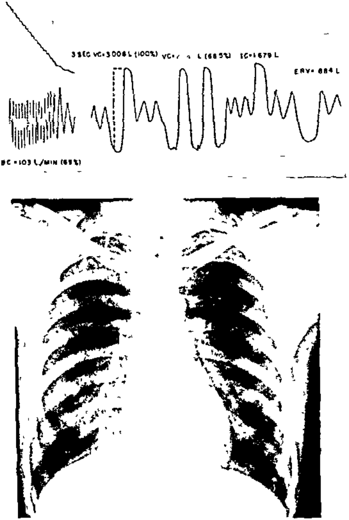


Fig. 17.9. Rheumatoid spondylitis coccidioidomycosis (with cavitation in right
[upp]er lobe). In upper figure, middle reading is VC = 2.740 L. (66.5%)
J. C. 24-year-old male. *Chief complaint:* Mild chronic cough with hemoptyses
[...] 6 months. *Additional pulmonary function data:* RV/TLC × 100 21%

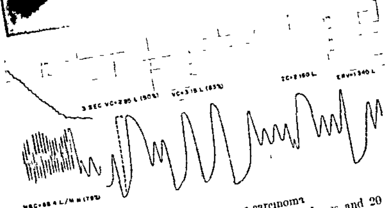
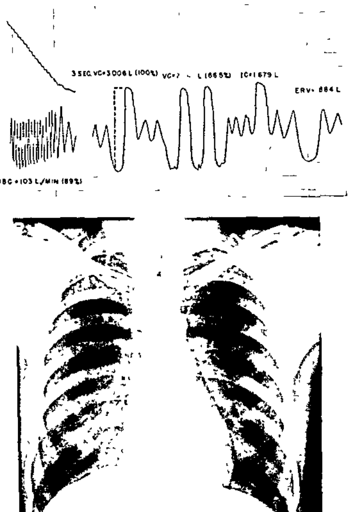


Fig 17 8 Bronchogenic carcinoma

C. C 58-year-old male *Chief complaint:* Cough, wakness and 20 pound weight loss for 5 months. *Additional pulmonary function data* RV/TLC × 100.8%, S_{aO_2} 94.7%, C_{aCO_2} 52 5 vol %.



ig 17 9 Rheumatoid spondylitis coccidioidomycosis (with cavitation in right
er lobe) In upper figure, middle reading is VC = 2 740 L (66 5%)
C 24-year-old male *Chief complaint* Mild chronic cough with hemoptyses
6 months *Additional pulmonary function data* RV/TLC × 100 21%

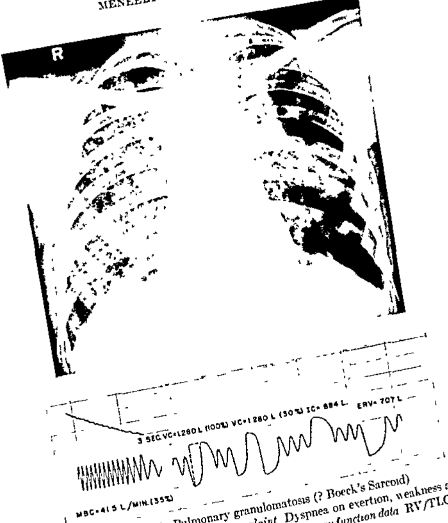


FIG 17 10 Pulmonary granulomatosis (? Boeck's Sarcoid) A S 30-year-old male *Chief complaint* Dyspnea on exertion, weakness and 20 pound weight loss for 2 years *Additional pulmonary function data* RV/TLC × 100 26%

versible obstruction may be found in cardiac dyspnea and, indeed, sometimes in pulmonary fibrosis without emphysema The physiologists associated with McCann at the Cardio-Respiratory Laboratory of The University of Rochester were able to distinguish two forms of chronic pulmonary distention, one primarily obstructive in origin, the other, which formerly had been called

senile emphysema, they recognized as largely postural in origin The "compensatory" emphysema which develops as nodular forms of silicosis undergo conglomeration is probably more due to stretching and space-filling than to "obstruction" as such The characteristic defect in chronic pulmonary distention (Figs 17 11,

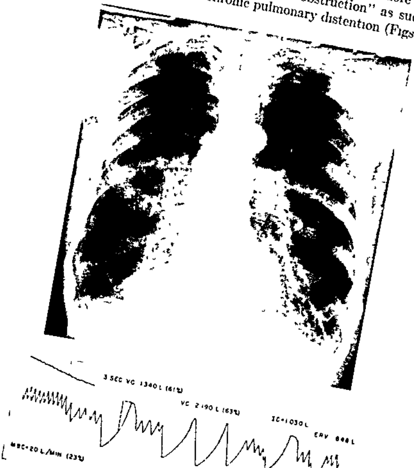


Fig 17 11 Pulmonary emphysema and pulmonary fibrosis
J A 58-year-old male *Chief complaint* Progressive exertional dyspnea and cough for nine years *Additional pulmonary function data* RV/TLC × 100 48%

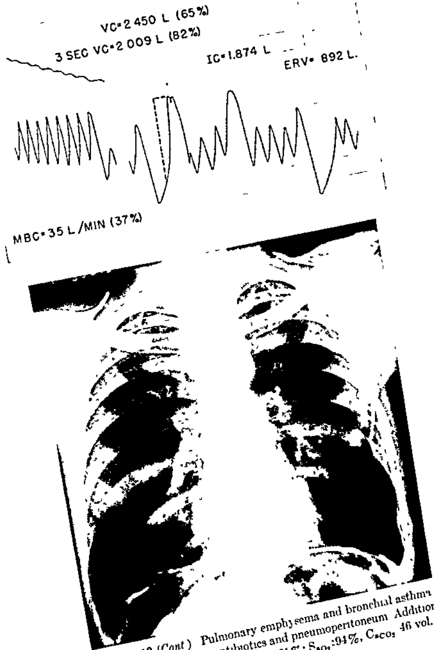


FIG 17 13 (*Cont*) Pulmonary emphysema and bronchial asthma B After bronchodilators, antibiotics and pneumoperitoneum Additional pulmonary function data RV/TLC × 100 61%; S_{aO_2}:94%, C_{aCO_2} 46 vol. %

chanics, flat diaphragms and, often, bronchiolar obstruction as well To refer to changes seen in this disorder as "obstructive ventilatory defect" is an oversimplification The term chronic pulmonary distention should come back into wider use and the term "obstructive defect" be reserved for those instances where it is demonstrable

To carry ventilation studies beyond graphic respirometry one should measure *functional residual capacity* By deducting expiratory reserve volume from it, one obtains the residual volume of the lung Changes in residual volume are most characteristic in pulmonary emphysema, providing the best means of estimating the degree of pulmonary distention which is present at the moment Pulmonary distention is by definition a relative or absolute increase in the amount of air which is not usually (functional residual capacity) or which cannot be (residual volume) expelled from the chest by expiration Total capacity is often also increased It is a simple matter to measure FRC and RV We have developed a greatly simplified version of the closed circuit helium method introduced by one of us in 1941 That procedure, which was much like McMichael's version of the hydrogen method, was subsequently compared with other methods by one of us (1949) and others (Gilson and Hugh-Jones) Fowler concludes that in comparison with other methods in common use " greater precision appears possible with closed circuit methods using serial helium or nitrogen analysis "

Figure 17.14 illustrates the apparatus on a crank-adjustable "over the bed" hospital table The added Helium Analyzer in no way interferes with the ordinary uses of the respirometer Still more recently we have substituted a motor driven blower for the "J" valves seen in Figure 17 14 and in the circuit diagram (Fig 17 15) A blower so greatly reduces breathing resistance that the instrument is improved considerably for measurement of maximum minute ventilation. With a constant current power supply and blower circulation the shape of the mixing curve is obtained Intrapulmonary gas mixing may be evaluated from it in any one of several ways The equipment illustrated in Figure 17 14 is in itself an adequate resource for practically all routine ventilation

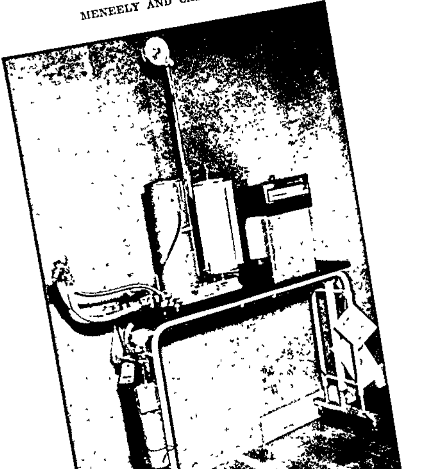


Fig 17 14

studies If arterial blood gas analysis is also made available, routine pulmonary function studies of a fairly detailed sort may be accomplished without additional instrumentation.

The simple procedure for FRC by the closed circuit helium method is illustrated in Figure 17.16 An example of the tracing obtained and the calculations are shown in Figure 17 17 Results are highly reproducible as demonstrated in Table 1 The large variability of FRC in patients with severe grades of chronic pul-

monary distention (FRC more than 5 liters) is probably real Certainly it is noted, with any method, that on some days consistent values different from those found other days occur.

In the past much has been made of possible errors in FRC due to breathing from decreasing concentrations of oxygen. The principle upon which this objection is based is sound and may be demonstrated by comparison between groups When data is analyzed statistically by individuals rather than by groups it is quickly evident that variance within determinations on the individual is larger than the differences attributed to the decreasing oxygen concentration Actually, the original Christie nitrogen method and the methods introduced since all give values entirely satisfac-

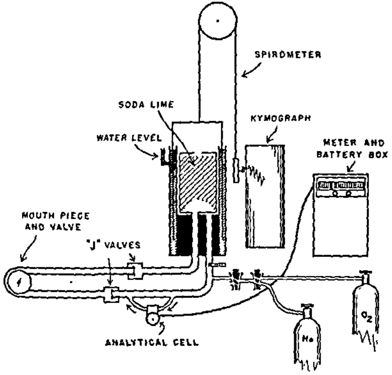


FIG 17.15 Closed circuit helium functional residual capacity

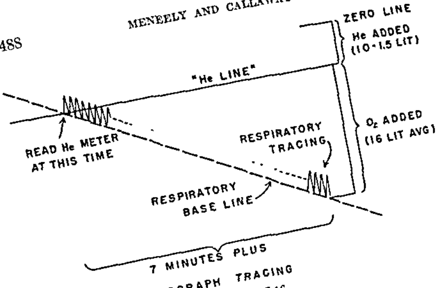


FIG 17.16.

Procedure.

Rinse spiro with room air

1. Bring bell to "zero" volume and close valve
2. Admit 1 0 to 1 5 liters helium and inscribe "He Line"
3. Add enough O_2 for 7 to 10 minutes breathing
4. Start kymograph and then connect subject
5. Read helium meter at the time the respiratory baseline crosses the "He Line"
6. Record bell temperature for correction of volumes to BTPS
7. Inspiratory capacity and expiratory reserve volume are then measured for the lung volume calculations on the same spirometer with subject in same position as for FRC usually semi-recumbent
8.

tory for clinical use Calculating the effect of an "error" on the end result of the test upon which interpretation is to be based is instructive Such a calculation is shown in Table 2. Substantial volumetric "errors" change the ratio of residual volume to total capacity by insignificant amounts.

The biologic variation in the volume of the lung and its fractions is unfortunately large Normal standards based on sex, age and stature have a coefficient of variation in excess of 25 per cent. This large normal variation is principally due to variation in the anatomic location of the diaphragm which seems impossible to determine by external measurement Normal standards for the

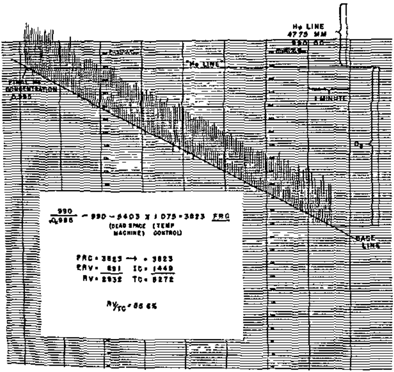


FIG 17 17

Calculations:

$$\text{Dead space} = \frac{\text{He added}}{\text{Final He Conc}} - \text{He added}$$

$$\text{F R C}^* = \frac{\text{He added}}{\text{Final He Conc}} - \text{He added} - \text{Dead space}$$

* This volume must be corrected to the observed baseline in the respiratory tracing, otherwise errors up to 600 ml or more may result

lung volume and its fractions (including vital capacity) should be viewed with considerable skepticism The best method for predicting normal values, developed by Hurtado and Fray, requires planimetric measurement of chest x-rays and has never become

TABLE 1

Reproducibility of the functional residual capacity
(based on difference between first and second of 42 serial duplicate estimations with P = 0 05)

For all values of FRC (n = 42, σ = 121 ml)	
Difference should not exceed	245 ml
"Error" of mean	±86 ml
For FRC less than 5 liters (n = 29, σ = 75 ml)	
Difference should not exceed	153 ml
"Error" of mean	±54 ml
For FRC more than 5 liters (n = 13, σ = 176 ml)	
Difference should not exceed	385 ml
"Error" of mean	±136 ml

TABLE 2

Effect of an "error" on ratio of residual to total capacity

In a normal subject with FRC = 2 0 l , ERV = 0 8 l and VC = 3 6 l an "error" of 200 ml in FRC would change the ratio from 25% to 28%	+3 0%
In a patient with emphysema with FRC = 5 0 l , ERV = 1 2 l and VC = 2 55 l an "error" of 400 ml in FRC would change the ratio from 60% to 62 5%	+2 5%

popular for routine use The ratio of residual volume to total capacity expressed per cent is probably more reliable than absolute values of the fractions A rule of thumb for the mean normal value of this ratio in males is that it should be 20 per cent until age 40 and thereafter equal to one-half the age The normal range is plus and minus forty per cent, *i e* , the upper limit of normal is 28 per cent until age 40 and rises gradually thereafter to 42 per cent at age 60 The traditional upper limit of normal (35 per cent for men of all ages) is too high for younger and middle aged men. Women consistently exhibit higher values

Correlation of the ratio of residual volume to total capacity with autopsy findings has often misled investigators who failed to distinguish between pulmonary distention and obstructive defect. In the apt phraseology of Cournand and Richards the lung volume measurement describes the air space available for ventilation It cannot be appraised at autopsy and the anatomic alterations sometimes considered characteristic of "pulmonary emphysema"

by the pathologist relate poorly to the volumes observed in the living McCann comments that medicine has come out of the deadhouse The collapsed, fixed and stained, 1 sq. cm sample of lung tissue commonly used for microscopic anatomic diagnosis is a miserable caricature of the delicately beautiful elastic dynamic structure of the living breathing lung In few areas is traditional morphology separated by a wider abyss from physiologic actuality than in the respiratory apparatus and its function

It is not to be supposed that precise arterial blood gas analysis will soon be available in every doctor's office or even in every hospital Nevertheless, understanding of the behavior of the blood gases in disease is imperative to good clinical practice and most especially among patients with chronic respiratory disease In the last analysis, the purpose of external respiration is oxygenation of the blood and controlled CO_2 excretion Analysis of arterial blood for oxygen saturation, for CO_2 content and, when possible, for pH and CO_2 tension can be the real "test" of pulmonary function Understanding of the diffusion-perfusion relationship is extremely important but beyond the scope of this chapter The reader is referred to other chapters of this volume and to Comroe's beautifully lucid and readable dissertations on the subject

To distinguish between alveolocapillary gas diffusion defect and shunting of circulation through nonaerated pathways is difficult For routine pulmonary function studies it suffices to measure the blood gases at rest, after exercise and, sometimes, after pure oxygen breathing The most widely used and still the most reliable method is direct arterial puncture using the Cournand needle Blood is drawn and stored under ice water in a heparinized silicone greased syringe The classical manometric Van Slyke apparatus analytic methods detailed in volume 2 of the original edition of Peters and Van Slyke's "Clinical Chemistry" have not been significantly improved except as to the manner in which blood is drawn and stored Manometric methods are difficult to learn from reading alone It is best to visit a laboratory accomplished in these analyses, or, as a poor substitute, to send a technician to such a laboratory for training Methods deteriorate when passed from technician to technician The routine analytic work in a laboratory

NORMAL

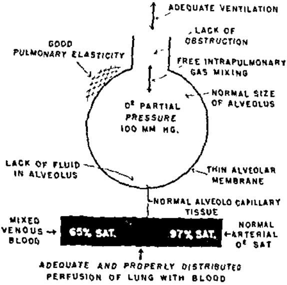


FIG. 17.18 *Normal* Determination of the arterial oxygen saturation is useful in the evaluation of patients with pulmonary disease The primary factors which govern the arterial oxygen saturation and likewise, the factors which may be evaluated by a determination of the arterial oxygen saturation are: ventilation, *intrapulmonary gas mixing, diffusion, and perfusion. Measurement of the arterial* oxygen saturation is useful as an overall test of the four factors listed above but will not delineate specific impairment of these functions. Combined with other studies it is helpful in the separate evaluation of the four factors More elaborate blood gas studies are necessary for specific delineation, especially of diffusion and perfusion Although the arterial oxygen saturation is useful in assessing the ability of the lung to oxygenate blood, it is not the most sensitive measure of this function. More elaborate blood gas studies may reveal impaired diffusion in some patients who have normal arterial oxygen saturation

is not likely to be of high quality unless continually sustained by the physician in charge who can do so only if he is (or formerly was) expert himself in technique.

Factors which importantly affect normal arterial oxygen saturation are summarized in Figure 17.18 The manner in which these

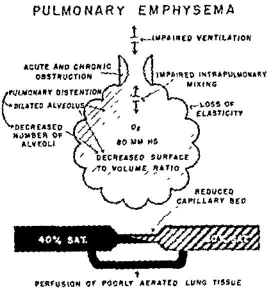


FIG. 17 19 *Pulmonary emphysema* In the usual case of pulmonary emphysema with arterial oxygen unsaturation no single function is wholly responsible for the impairment of oxygenation Usually, ventilation, intrapulmonary gas mixing, diffusion, and perfusion are all impaired and it is not possible to quantitate impairment of any one function Determination of the arterial oxygen saturation in pulmonary emphysema is frequently used in combination with the measurement of arterial carbon dioxide content for classification of the severity of the disease This is especially true when the measurements are made during exercise as well as at rest In addition, serial determinations of arterial oxygen saturation in any given patient with pulmonary emphysema are helpful in determining the type of therapy and evaluating its effectiveness

Controlled CO_2 elimination is as important a function of respiration as oxygenation When CO_2 is released from body cells into the blood it forms H_2CO_3, an acid This acid combines to some extent with the base of blood Depending upon the amount of base and upon the amount of CO_2, there will be more or less "free" dissolved CO_2. *CO_2 tension* (partial pressure of CO_2) is the measure of "free" carbon dioxide. *pH*, the measure of relative acidity or alkalinity of the blood, is dependent upon the amount of base and the amount of CO_2 in the blood at the moment

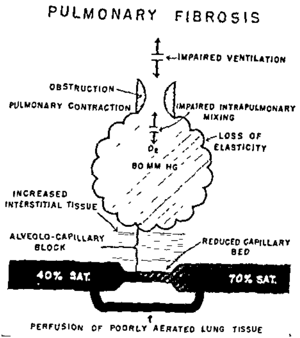


FIG 17 20 *Pulmonary fibrosis* In pulmonary fibrosis, there may be much variation in impairment of pulmonary function Thus, the arterial oxygen saturation in patients with different types of pulmonary fibrosis is highly variable In those cases of pulmonary fibrosis which lead to airway obstruction, pulmonary emphysema is frequently found

The arterial oxygen saturation will be influenced not only by the basic lesion but also by the factors discussed under pulmonary emphysema In some patients with pulmonary fibrosis, diffusion of gases across the alveolocapillary membrane is the only significant lesion (The alveolocapillary block syndrome) Measurement of the arterial oxygen saturation may be most helpful here for it may be the only commonly determined measurement which is significantly impaired

In addition to the specific classes of pulmonary fibrosis discussed above, there are cases of pulmonary fibrosis with no impairment of oxygenation of the blood Thus, a normal arterial oxygen saturation may be helpful

Since CO_2 is highly diffusible, the CO_2 tension of arterialized blood leaving an alveolar capillary network is almost exactly the same as the CO_2 tension of the gas in that alveolus. This remains true even when alveolocapillary oxygen diffusion is severely impaired because CO_2 is much more highly diffusible than oxygen Alveolar CO_2 tension therefore "controls" arterial CO_2 tension,

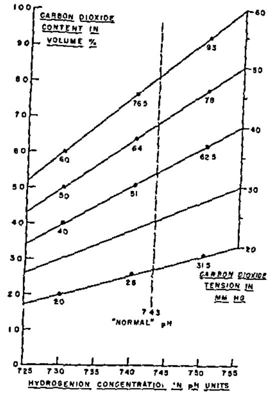
even in advanced pulmonary impairment Alveolar CO_2 tension in turn depends upon the quantity and quality of ventilation and intrapulmonary gas mixing

The amount of base in the blood is controlled principally by the kidney It normally retains extra base (principally sodium) when pH shifts toward the acid side This compensatory renal process is slow (days) compared to the pulmonary regulation of alveolar CO_2 (seconds) The pH of the blood is directly dependent upon the relative amounts of CO_2 and base present The retention or excretion of base by the kidney may be regarded as the "fundamental" factor in acid-base balance, but pulmonary regulation of alveolar and so of arterial CO_2 tension is the "immediate" factor since normally it can alter alveolar CO_2 and so arterial CO_2 almost instantaneously From moment to moment, then, pulmonary regulation of CO_2 tension is the major factor in maintaining blood pH Serious consequences rapidly result if blood pH is not held virtually constant at 7 43 Therefore, it is not enough for the lungs merely to eliminate CO_2 from the body, they must do it in such a manner that blood pH is controlled within narrow limits

There are many methods to measure arterial CO_2 tension and arterial pH For the pulmonary physiologist the easiest adequate method depends upon certain relations which have been found to exist between arterial pH, CO_2 content and CO_2 tension The CO_2 content of an arterial blood sample can be measured with the Van Slyke manometric apparatus and its pH measured directly with a glass electrode pH meter With this information arterial CO_2 tension can be read from a graph (Fig 17 21)

In pulmonary function testing, arterial pH determination is of importance largely because when it is known and when arterial CO_2 content is known, arterial CO_2 tension may be derived This latter is closely related to alveolar CO_2 tension which in turn is an excellent measure of the adequacy of ventilation and intrapulmonary gas mixing (Figs 17 22, 17 23)

CO_2 has been called the "respiratory hormone" because usually it is the most potent factor in control of respiration Increases in blood CO_2 normally result promptly in stimulation of ventilation and consequent washing out of excess CO_2 Inadequate ventila-



RELATION OF CARBON DIOXIDE TENSION, CARBON DIOXIDE CONTENT AND pH

FIG 17.21

(Graph prepared by Donald S Tysinger, Jr., M D)

tion for whatever reason results in CO_2 retention. Acutely this causes lowering of pH known as respiratory acidosis If CO_2 retention persists as may occur in chronic pulmonary insufficiency, renal retention of base raises pH to normal compensating for high CO_2 tension In such cases, the respiratory center becomes insensitive to CO_2 Anoxia is invariably present in chronic pulmonary insufficiency with CO_2 retention and is then the main stimulus to ventilation Under these conditions, oxygen therapy may abolish anoxia and respirations may be profoundly depressed as a result of withdrawal of the only adequate existing stimulus

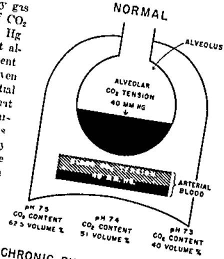


FIG 17 22 *Normal* With normal ventilation and intrapulmonary gas mixing, the partial pressure of CO_2 in the alveoli is usually 40 mm Hg Normally there is no significant alveolar-arterial blood CO_2 gradient Thus, for blood leaving any given pulmonary capillary the partial pressure of carbon dioxide in that capillary will be the same as the partial pressure of CO_2 in that alveolus With normal alveoli and pulmonary capillaries throughout the lung the partial pressure of carbon dioxide in arterial blood is 40 mm Hg With a normal blood base, the pH will be normal

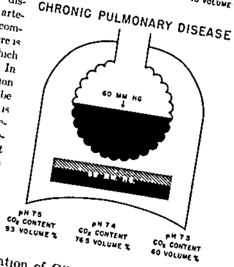


FIG 17 23 *Chronic pulmonary disease* In chronic pulmonary disease the usual abnormality of arterial CO_2 and pH is that which accompanies hypoventilation Thus, there is usually a respiratory acidosis which may or may not be compensated In addition, by the time CO_2 retention and acidosis occur, anoxia will also be present In these patients, anoxia is the main stimulus to ventilation because the respiratory center has become insensitive to CO_2 Abrupt administration of high concentrations of oxygen depress respiration Further retention of CO_2 may occur rapidly and lead to CO_2 narcosis and even death if steps are not taken to insure adequate ventilation

to ventilation Further accumulation of CO_2 may occur rapidly (within minutes) and lead to CO_2 narcosis and even death if steps are not taken to insure adequate ventilation

Since retention of base is a feature of chronic CO_2 retention and because pH is usually held close to normal, the plasma CO_2 com-

bining power which measures plasma base is increased in close proportion to the CO_2 retention Since determination of plasma CO_2 combining power is almost universally obtainable on an emergency basis, it can serve to identify those anoxic patients in whom oxygen therapy without artificially maintained ventilation may be disastrous

Emotion, drugs, central nervous system disorders, high altitude (hypoxia) *and other factors may cause hyperventilation. In this* case, alveolar CO_2 is "blown off" excessively. The resulting de-

FIG. 17 21.

PULMONARY FUNCTION REQUEST

Patient's name Age Ward Reg No
Date requested Date report desired
Date tests completed Date report sent to ward
Requisition made by Doctor

---

1 Diagnosis
2 Estimation of degree of pulmonary insufficiency *(check one)*
(a) None (b) Slight (c) Moderate (d) Severe
3 Dyspnea (check one)
(a) None (b) With moderate exercise (c) With mild exercise
(d) At rest
4 Please check any of the following disease processes suspected here
(a) Pulmonary emphysema (b) Bronchial asthma
(c) Bronchiectasis (d) Chronic bronchitis (e) Infiltrative process (the or other)
(f) Consolidation (g) Atelectasis (h) Diffuse pulmonary fibrosis
(i) *Pleural disease (fibrothorax, etc)* (j) *Other (specify)*

5 Has the patient ever had pneumothorax (Yes) (No), Pneumoperitoneum (Yes) (No), phrenic crush (Yes) (No)
6 Previous thoracic surgery
(a) Procedure Date
(b) Procedure Date
7 Contemplated thoracic (or other) surgery
(a) Procedure When contemplated
8 Medications *(check those patient is receiving):*
(a) Narcotic (b) Bronchodilator, oral (c) Bronchodilator, nebulized
(d) Expectorants
9 Please indicate the particular information about the patient which you desire from these tests

10 Previous pulmonary function studies (Yes) (No)

FIG. 17 25.

Age yrs Ht ft in Wt lbs Body Surface Area M²

I Ventilation Measurements

	Pred	Observ	% Predicted	After Bronchodilator
Vital capacity (VC), total liters				
1 sec VC, % of total	70+			
2 sec VC, % of total	80+			
3 sec VC, % of total	90+			
Expiratory reserve volume				
Inspiratory Reserve Capacity				
Total VC time, sec	<4			
Mid half VC liter time, sec, l	0 85			
Maximum breathing capacity (MBC), l/min				
Respiratory rate				
MBC baseline level				
Breathing reserve (BR) = MBC-RMV l/min	<0			
BR/MBC × 100	90+			
Air velocity index = $\frac{\text{\% Predicted MBC}}{\text{\% Predicted VC}}$	1 0			

II Lung Volume Determinations

	Predicted	Observed	% Predicted
Functional residual capacity, ml			
Expiratory reserve volume, ml			
Residual volume, ml			
Inspiratory capacity, ml			
Total capacity, ml			
RV/TC × 100, %			
Physiologic dead space, ml			

III Blood Gas Determinations

	Predicted	Observed	Standard Exercise
Arterial O_2 capacity, vol %			
Arterial O_2 content resting, vol %			
Arterial O_2 saturation resting, %			
Arterial CO_2 content, vol %			
Arterial pH			
Arterial CO_2 tension			

creased arterial CO_2 tension occurring thus acutely (*i.e.*, without time for renal readjustment of base) results in an increased pH. This situation is known as respiratory alkalosis. *This rarely occurs* as a result of chronic pulmonary disease but is of importance in understanding pulmonary function in certain situations such as that of the respirator patient.

There are many other tests of pulmonary function. Those described in this chapter are well established. Most of the actual work can be done by a well trained technician. This permits development of a service facility to which patients may be referred *routinely, much as is the case with routine electrocardiography.* A form of request for pulmonary function tests which has proved fairly satisfactory in our laboratory for several years is reproduced in Figure 17.24. The form we have found useful for reporting results of tests is reproduced in Figure 17.25. Special tests may be devised to bring out particular points in particular patients. There is no limit to the opportunity for ingenuity on the part of the physician-physiologist. The fact remains, the best approach to the problem, *the one most likely to lead to continued and useful* service is to make a modest start with reliable equipment and simple tests. When such a laboratory is functioning smoothly and simple factual reports are returning promptly to the referring physicians, there is time enough to modify, to improvise, to elaborate, to expand, to complicate and, perhaps, to advance. By that time, the value of the steady flow of factual information derived from simple tests carefully performed and conservatively interpreted will be so *well established there will be no question* whether routine function tests should be continued and the soil will perhaps be more fertile to grow a larger plant.

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Chapter 18

DISCUSSION AND SUMMARY

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Medical and population trends predicted by life insurance companies indicate the degree to which pulmonary emphysema may be expected to increase with the increasing longevity of the general population. In 1900 there were 23 million Americans over 35 years of age, today there are 70 million and in 1965 it is estimated that there will be 81 million. The number of people over 65 today is 14 million, and it is estimated that this will increase to 21 million in 1975. In other words, there will then be almost as many people living over 65 as were recorded in 1900 alive over 35 years of age.

The importance of loss of physical fitness as a factor which in itself produces dyspnea is borne out by the clinical material cited in Chapter 4 on senile emphysema. Thus, Thewlis is quoted as saying that wasting and degeneration of the muscles of the chest wall take place in older people, the greatest atrophy being present in the intercostal muscles and the diaphragm. Nascher and Rollston state that the primary degenerative change in the lungs of individuals in advancing years is atrophy, a diminution of their size and weight. Kaltreider reports that the decrease in vital capacity observed in men over the age of 50 was less marked in those who continued to be active. The available evidence does indeed strongly suggest that the atrophic process is not only linked with an inactive or sedentary existence but also that it may to some degree be diminished by physical exercise, properly regulated in relatively normal individuals, and facilitated in those with pulmonary emphysema by the inhalation of oxygen, with corresponding decrease in shortness of breath on exertion.

Knight and White have called attention to the clinical evidence which supports the belief that bronchial infection, especially of the bronchioles, at times plays a role in the cause of pulmonary emphysema An infectious bronchitis may lead to a bronchitis obliterans with obstructive distention of the alveoli. Smoking, mentioned in the literature as a pathogenetic factor, requires more convincing statistical and other studies to support such a contention It is true that chronic bronchitis with a productive cough appears to be related to inhalation of cigarette smoke in a small minority of such cases The percentage of patients in whom smoking is held responsible for chronic bronchitis has been variously estimated to be between 2 and 7 per cent and in some quarters much higher Patients with pulmonary emphysema seen in our clinic are not usually benefited by giving up cigarettes; the urgent advice so commonly prescribed to give up the smoking of cigarettes is not generally justified by the benefit obtained, especially in comparison with the therapeutic aids now available. It may be, as Trimble said to us, that we too frequently see a more advanced form of the disease since other observers report more improvement from cessation of smoking than we observed in a three year study as well as subsequently.

Knight cautions that it is important not to overlook pulmonary carcinoma, heart failure, tuberculosis and mycotic infection in patients with bronchitis Unfortunately, I have seen cases of each of these entities, in which advice to give up smoking was followed by amelioration of symptoms but also by progression of the underlying disease Since the majority of so-called "cigarette coughs" are the result of organic pathology, a diagnosis of the basic condition should be sought for The fact that the cough clears up as a result of removal of this trigger mechanism is apt to be interpreted as a cause and effect relationship but some months later the signs of left ventricular failure, cancer of the lung, suppurative or allergic bronchitis may reveal the actual diagnosis Since cough is nature's method of clearing the upper respiratory tract of foreign substance, its effect as a helpful procedure need not be overlooked in cases in which the inhaled smoke does not

produce the mucus itself Many of the effective bronchodilator aerosols also initiate a cough

The studies of Riley, Alexander, Chernuack and Daymon here presented indicate that impairment of diffusion of oxygen and carbon dioxide across the pulmonary membrane is a much less important factor in the production of dyspnea than the ventilatory disturbance Decreased or normal compliance is found in the early part of the inspiratory cycle and the bullous parts of the lung fill readily It is only when the lungs are quite thoroughly inflated that marked increases in thoracic pressures are required to overcome the elastance of the pulmonary parenchyma The deficient elastic recoil of the lungs is, however, a factor which promotes bronchial closure because of the impaired outward traction on the pulmonary membrane surrounding the smaller bronchi, as illustrated in Chapter 9 by Daymon, when the intracanalicular pressure is low Overdistention of the alveoli is the characteristic result of expiratory collapse of the bronchioles and their related tubal connections, bronchial constriction is not only due to bronchospasm itself, but also apparently to an increased tonus of the hypertrophied muscles surrounding the smaller bronchi as well as to the occlusive effect of retained bronchial secretions As lung volume decreases in expiration the rate of expiratory flow becomes sharply diminished Under these circumstances impaired elastic recoil of the lungs combined with bronchial narrowing tend to produce trapping of air and progressive distention of the alveoli

This disturbance in pathologic physiology leads to overventilation of relatively poor functioning elements of the lungs near the periphery of the chest The therapeutic procedures which tend to restore better alveolar ventilation include inhalation of bronchodilator aerosols which relieves bronchospasm, pressure breathing which maintains a larger lumen of the bronchial passageway, especially when it is carried out with an even pressure in inspiration and expiration, antibiotic and hormonal therapy, and effective elimination of bronchial secretions by enhancement of the effectiveness of the natural cough, the use of exsufflation and of

posture In Chapters 7 and 8 by Beck and Levine these methods of promoting bronchial drainage have been outlined The value of procedures which promote a redistribution of air from overdistended bullous areas to more normal pulmonary tissue at the hilum and lower lobes of the lung is described in Chapter 3 on Restoration of Diaphragmatic Function For many years it has been clear that procedures which elevate the diaphragm, as well as restore its convex shape, are followed by relief of dyspnea. Studies of the blood gases have now confirmed at least in so far as the headward tilt of the thorax is concerned, the more efficient ventilation that takes place with diaphragmatic breathing. It is therefore of considerable value to spend as much time as is practically feasible to educate the patient into the use of the diaphragm as well as an effective lower abdominal belt so that the intra-abdominal pressure and the diaphragm are thereby elevated

The various tests of respiratory function developed to record the physiologic disturbance in pulmonary emphysema have added to our understanding of the disease In our clinic, since spirometric records were employed between 1934 and 1938, the effectiveness of therapeutic procedures (the aim of which was to improve pulmonary function) has been frequently studied by measuring their effect on the pulmonary ventilation and the volume as well as the velocity of air flow in expiration The ventilatory difference between inhalation of air and 100 per cent oxygen appeared to be a reliable guide to the degree of overt or latent hypoxic dyspnea in many cases of pulmonary emphysema It was observed in our early studies that, after continuous inhalation of nebulized bronchodilator solutions had relieved bronchospasm, the characteristic decrease in ventilation in patients subsequently tested by breathing 100 per cent oxygen as compared to air was often more strikingly manifested. An increase in the expiratory air velocity and vital capacity recorded on a fast-moving drum provided good evidence of the relief of bronchospasm; these procedures have been extensively studied by many investigators and often reveal pathophysiologic changes similar to those recorded by the more specific study of flow rates through pneumotachygraphy.

Measurements of the minute volume of breathing during the

inhalation of air revealed that procedures which improved ventilatory exchange at times resulted in a significant decrease in minute volume, these procedures included continuous pressure breathing with air or, frequently, with 80 per cent helium and 20 per cent oxygen Relief of dyspnea was, in the majority of cases, correlated with the lowered pulmonary ventilation produced in cases of pulmonary emphysema, bronchial asthma, as well as partial obstruction of the larger bronchi or larynx It is of interest that many patients do not maintain their previous increased ventilation, which might further increase their arterial pO_2 and lower the pCO_2 since apparently relief of dyspnea assumes priority in these cases Although the mouthpiece and a tight nose clamp at times alter the natural resting ventilation of the patient, they appear to be necessary for accurate recording However, conclusions drawn on the effect of the therapeutic use of helium on subjective dyspnea with this procedure may be (and indeed has been) apparently responsible for erroneous conclusions

Miller, Fowler and Helmholz have contributed Chapter 10 with the intention of answering, in so far as it is possible, the question 'Does the administration of bronchodilators by IPPB offer significant advantages over standard aerosol techniques, and if so, in what type of patients is it applicable?" The studies which they presented revealed that in the majority of instances no superiority for the use of IPPB as a method of introducing bronchodilator aerosols into the lung could be demonstrated over methods previously used by which continuous nebulization of these increased amounts of epinephrine were employed In the early studies reported in this country by Richards and Barach, continuous nebulization of dilute solutions of epinephrine were reported to be of considerably more value than the symptomatic, frequently transient relief obtained by the hand-bulb nebulizer

Motley and his collaborators did not present comparative data on the previously employed techniques with their method of employing "Intermittent Pressure Breathing Treatments" In respect to the use of IPPB itself, Segal and associate, Wu and associates, and Miller and associates reported that IPPB, with air or with oxygen, was of little or no practical value in the treat-

viduals treated with IPPB are reported to have subjective improvement, Miller and associates observed that in the control series of patients in which a similar program of bronchodilator aerosol was used but without IPPB, 70 per cent also obtained subjective improvement. The only instances in which these authors noted objective improvement with IPPB which "suggests possible superiority to aerosol alone have been noted in younger patients, particularly those with more than ¼ cupful of mucoid or mucopurulent sputum daily This type of case represents a minority of the patients whom we see with pulmonary emphysema "

The physiologic effects of pressure breathing include a physical relief of asthmatic dyspnea An enlargement of the bronchial diameter during the period of its employment is present, more marked in continuous than in intermittent pressure breathing From this point of view it might be expected that some increased penetration of bronchodilator aerosols may be achieved but whether the procedure is much more successful than a deep breath has been questioned Pressure breathing may result in a more uniform enlargement of the bronchial tree. However, in a period of 15 minutes' inhalation it is likely that various parts of the bronchial system become patent, either during quiet breathing or with intermittent use of a deep inspiration

The principles of pressure breathing and of bronchodilator aerosol therapy have been presented in this volume from separate physiologic points of view. In Chapters 6 and 7 by Bickerman and Levine the techniques of simpler methods of inhaling dilute solutions of increased amounts of bronchodilator and bronchovasoconstricting solutions are described. It would appear reasonable and considerate advice to employ these techniques, which are simple in application and less expensive to the patient, before advice is given to purchase equipment which is not only originally costly but expensive in maintenance

It is of interest that Fowler and associates indicate that IPPB may impair venous return sufficiently in the presence of a failing

right ventricle to cause marked peripheral edema, since they have noted this complication in several patients with pulmonary emphysema. It has also been pointed out that, whereas pressure breathing is of value in left ventricular failure, it is hazardous in peripheral circulatory insufficiency, unless the blood pressure is carefully watched.

Increased alveolar ventilation, as pointed out in Chapters 11, 14 and 15 by Alexander, Chernack, and Richards and Fishman is critically important in the treatment of patients in whom CO_2 retention is the cause of symptoms due to respiratory acidosis. The principles and results of treatment are reviewed in these presentations, including the use of intermittent pressure breathing devices, the exsufflator and the tank respirator. We might add here that an additional objective, apart from increasing the total ventilation, is selective distribution of inspired air to the hilum and better perfused areas of the lungs, as accomplished by the headward tilt of the thorax and other procedures which elevate the dome of the diaphragm.

In our clinic, CO_2 retention in the presence of a normal pH is not necessarily an indication for mechanical hyperventilation. Other investigators, referred to in earlier chapters, consider CO_2 retention itself a pathogenic influence that merits the routine use of hyperventilation. Richards and Fishman, in Chapter 15 on cor pulmonale have discussed the increase in CO_2 found in the blood as representing both good and evil, homeostasis and "hyperexesis" (the "excess response"), good "because of the high CO_2 enables the metabolic CO_2 to be eliminated with relatively small total ventilation," evil "because a vicious cycle may be set up reducing progressively the respiratory stimulus, with pCO_2 increasing to the level of CO_2 narcosis." These authors give levels of CO_2 for which mechanical ventilation is indicated, such as when the arterial blood pCO_2 exceeds 65 mm. Hg, " . . . and especially if there is a considerable uncompensated respiratory acidosis as indicated by an arterial pH below 7.32."

The editors have been impressed by the adaptive mechanism through which increased arterial and alveolar carbon dioxide levels are in part responsible for an elimination of CO_2 in higher

concentration per unit volume of breathing. Under these circumstances, oxygen treatment appears to permit a decreased pulmonary ventilation without necessarily increasing acidosis itself. The fact that the arterial CO_2 may decrease while oxygen therapy is maintained is an indication that improvement in respiratory function is not only accompanied by decreasing CO_2 retention, but a decreased use of the adaptive mechanism previously employed The decrease in arterial CO_2 content effected without hyperventilation, but as a consequence of varied procedures which improve respiratory function itself appears to the editors to be a sound approach except in cases with an uncompensated respiratory acidosis in which intermittent pressure breathing and other allied mechanical methods of augmenting the respiration should be unreservedly carried out

Antibiotic therapy as described by Knight and White and by Levine, the use of prednisone, restoration of cardiac function, improved diaphragmatic function and other measures may be followed by a better exchange of O_2 and CO_2 with spontaneous fall in CO_2 of the arterial blood. The patient with mild or moderate CO_2 retention, in whom such treatment is responsible for reasonable improvement may have a compensated acidosis without symptoms, either from the increased pCO_2 or the increase in bicarbonate We have elsewhere called attention to the dyspnea caused by a lowered bicarbonate induced by hyperventilation in men in high mountainous regions when these subjects are returned to sea level It is our belief that a similar mechanism may become involved in some patients with pulmonary emphysema as a result of excessive lowering of base

That the increased work of breathing itself adds to the accumulation of CO_2, described by Cain and Otis and by Riley as the basis for the adaptive mechanism by which the body tolerates a rise in CO_2 tension, was mentioned in Chapter 14 by Cherniack The latter author reports original data which revealed that both the elastic and viscous work of breathing is reduced by administration of bronchodilator drugs and Beck (Chapter 7) showed that inhalation of these aerosols increased expiratory flow rates of the natural and mechanically induced cough, with an accompanying

increase in the clinical effectiveness of coughing. The relief of expiratory bronchial constriction is thus additionally confirmed as an important factor in the treatment of respiratory acidosis. Since these patients cannot voluntarily hyperventilate to the point of reducing their pCO_2, intermittent pressure breathing or exsufflation is indicated.

Acute CO_2 retention is accompanied by changes which manifestly are of harm to the patient, i.e., acid shift in pH and comatose states, as well as at times by high levels of serum potassium, with the symptoms and signs of hypercalemia, as mentioned by Cherniack. However, it is in the patient with chronic CO_2 retention that further studies appear to be indicated to determine in which cases the elevated pCO_2 may be the cause of injurious consequences and in which cases the high levels of arterial CO_2 serves the purpose of an homeostatic mechanism. Since Scott reported in 1920 that the increased buffering power of the blood and tissue fluids explained the reduced respiratory sensitivity to CO_2, studies have been carried out to explain this physiologic behavior of the patient with pulmonary emphysema, referred to in this volume by Cherniack, Alexander, Richards and Fishman.

In the studies reported from our clinic, the adaptive or homeostatic mechanism by which CO_2 is eliminated through maintenance of high arterial CO_2 tensions was observed in many of these patients without disturbance in mental function or pH, during the course of and following regulated oxygen therapy. In cases with chronic CO_2 retention, acid shift in pH has frequently been found, often when circulatory insufficiency or respiratory infection was added to the clinical state; in these cases, as stated by Cherniack and by Richards and Fishman, the reduction in CO_2 levels of the blood and tissues has been found to be of striking clinical value. This result has been achieved in some clinics without the use of oxygen and in others with the continuous administration of oxygen. IPPB is indicated with the use of 25 to 50 per cent oxygen or 75 per cent helium and 25 per cent oxygen rather than 100 per cent oxygen. Compressed air has been also recommended but some increase in oxygen concentration seems reasonable to combat hypoxia. The continuous inhalation of oxygen

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The control of chronic suppurative disease of the bronchi is indeed difficult. The etiologic agent may not always be determined by the methods now at our disposal In this country the Staphylococcus is frequently isolated whereas Mulder has described the *Hemophilus influenzae* as pathogenic in a high majority of cases Since antibiotic treatment results in some series of cases in the disappearance of organisms such as *Streptococcus viridans* and the Staphylococcus, as well as the disappearance of the *H influenzae* organism, this method of determining the actual cause of infection does not offer certain proof. It would appear that since the special methods required for cultivating the more fastidious strains of *H influenzae* are not commonly employed, variations in the reports of sputum cultures may be traced to varying technique A variety of micro-organisms will disappear from sputum cultures with the use of broad spectrum antibiotics, especially when combined with administration of streptomycin

Sensitivity studies are nevertheless indicated. In many cases a sample of sputum may be streaked on a blood plate and the various sensitivity disks then placed on the sputum smear. If a large area of inhibition is found around a disk, the drug which revealed this inhibiting effect may be found clinically useful Unfortunately, the problem is not simply determined in that way since some of the organisms may be suppressed but others may grow in varying degree around the disk However, if the sputum changes from purulent to mucoid during antibiotic therapy the program which was responsi[illegible] alteration sh[illegible] ntinued. Sensitivity tests at this [illegible] be mislead[illegible] he pathogenic agent may no longe[illegible] in the sp[illegible] s and the organisms which then [illegible] be [illegible] l not the cause of infection In [illegible] ce a [illegible] bacterial flora may cultivated [illegible] s of th[illegible] invasion. [illegible] spu[illegible] comes [illegible] n t [illegible] lary [illegible] may [illegible] and [illegible] sted

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In many cases of chronic infectious bronchitis, a trial of penicillin by mouth in a dosage of 1 to 2 million units a day is worth while, especially in cases in which no allergic reaction to the drug has been previously found. Even though gram-negative and gram-positive organisms may be grown in sputum cultures, the elimination of gram-positive bacteria, either the Staphylococcus, or in certain cases, the *Streptococcus viridans*, is at times followed by corresponding clinical improvement. This may be manifested by a decrease if not a disappearance of the purulent character of the sputum. Levine has described the frequent clinical effectiveness of penicillin treatment by aerosol, as well as the fact that it may be continued for long periods without bowel disturbance. In the event that the sputum suddenly becomes purulent, the broad spectrum antibiotics with streptomycin may then be employed.

Among the additional aids to elimination of infection, the attempt to improve bronchial drainage has been emphasized in this book by Beck and Levine, including especially the use of exsufflation. We have in fact observed that discontinuance of antibiotic treatment and institution of vigorous measures to promote elimination of previously retained bronchial secretions was followed in a few cases by the clearing of infection, including secondary invasion by the organisms that may develop in the wake of vigorous broad spectrum antibiotic therapy.

The use of erythromycin appears to be especially valuable in the case of *Staphylococcus aureus* infections that are resistant to other antibiotic agents, or that develop following broad spectrum antibiotic treatment. Neomycin has been employed intramuscularly for a period of 8 to 10 days without ill effect, but it is worth while to point out that administered by aerosol the drug is not absorbed to any significant degree into the circulation. This latter method of administration has been used for periods of 2 to 3 weeks or more in a dosage of 1.0 to 2.0 gm. daily without evidence of toxic effect and at times with a good therapeutic response against organisms that failed to react to the previously employed antibi-

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The increasing interest in the employment of surgical procedures in patients with pulmonary emphysema has been made the basis of Chapter 16 by Deterling, in which the criteria and results of the various measures proposed have been described. It is now clear that excision of bullous or cystic disease of the lung is followed by clinical improvement, often of marked degree Increasing experience in the use of diagnostic methods of determining the site and extent of the more diseased parts of the lung will undoubtedly stimulate further attempts to relieve the dyspnea of these patients by surgical procedures A redistribution of air to more normal parts of the lung undoubtedly follows the extirpation of bullous relatively nonfunctioning tissue Perhaps the use of prednisone to place the patient in an optimal state of lung function by relieving bronchospasm may be of help in operations of this kind It would seem to the writer that the argument to allow the lung remaining after removal of the diseased portion to expand is more sound than the employment of space fillers. This point of view is supported by the evidence described by Deterling, as well as by the studies referred to by Beck and the writer.

In Chapter 8 by Levine, the importance of combined antibiotic aerosol therapy and bronchial drainage is emphasized The improvement obtained by the use of exsufflation in cases of pulmonary emphysema was described not only in cases of suppurative bronchitis or bronchiectasis but in those with mucoid sputum as well The result of inflating previously unventilated alveoli by high inspiratory pressures was considered of special value in promoting drainage His studies confirm the safety of this procedure.

It is of interest to mention that aerosol therapy not only results in high antibiotic sputum concentrations not accomplished by systemic therapy, but that the parenchyma of the lung itself is reached by the antibiotic when administered in adequate dosage, in part through the drug absorbed locally and in part as a result of the blood concentration achieved by means of alveolar absorption

With the use of the precautions outlined in Levine's chapter, the side effects at times encountered appear to be prevented in

the majority of cases In cases in which the infection is controlled by 500,000 units of penicillin daily, with or without 0 5 gm of streptomycin, inhaled as an aerosol in divided doses, the bowel complications of broad spectrum antibiotic therapy have not been encountered, since the normal stool flora are little altered if at all

Bickerman has properly stated that the use of prednisone is preferred to that of cortisone because the newer steroid does not result in salt and water retention in dosages ordinarily required for the treatment of pulmonary emphysema In the older age group passive pulmonary congestion, of moderate or of slight degree, was not infrequently due to cortisone administration but even in cases of cor pulmonale and left ventricular insufficiency this complication has not been encountered as a result of prednisone treatment However, the aim of therapy should be the relief of severe bronchospasm by the combined employment of bronchodilator drugs, aerosols and potassium iodide as well as prednisone, and not simply prednisone alone Many years of experience have demonstrated the relative harmlessness of the older procedures which have been prescribed for the relief of asthmatic dyspnea, and, therefore, they should be primarily relied upon for maintenance therapy whenever possible in addition to the symptomatic benefit they may exert during the employment of prednisone for the control of more severe impairment of respiratory function Even in cases in which long-continued prednisone treatment is desirable, the use of bronchodilator medication and other allied drugs should be continued in order to decrease the dosage of the steroid hormone to a minimum This means that the patient is informed that wheezing of some degree is desirable provided that ingestion of aminophylline and or ephedrine and inhalation of nebulized epinephrine produces adequate relief The patient who is pleased with the fact that he can dispense with the nebulizer and other drugs is overdosed with steroid therapy My opinion is based on the fact that a smaller requirement of prednisone is thereby possible An additional safety factor is provided by routine administration of aluminum hydroxide or calcium carbonate two hours after meals and at bed-time Of 100 patients or more

on this program none have developed gastric or duodenal ulcer, as disclosed by symptoms However, gastrointestinal x-rays have been performed in only 15 per cent of this group

The factors resulting in the development of cor pulmonale have been vividly described by Richards and Fishman. The restriction and altered distensibility of the pulmonary vascular bed, arterial hypoxemia and polycythemia with hypervolemia are emphasized, the latter two are especially susceptible to treatment Since acute hypoxia of sufficient degree consistently elicits pulmonary hypertension, measures to reduce the factor of oxygen-want are indicated The range of these procedures is wide indeed, as has been previously discussed, as well as in respect to oxygen administration, especially its employment by a continuous rather than an intermittent technique

The value of repeated small phlebotomies in cases with polycythemia has been stressed only in cases with evidence of increased blood volume, *i e*, the congestive failure state. Polycythemia of moderate degree is not in itself an indication. Digitalization, low salt diet and the mercurial diuretics are indicated as in other forms of cardiac insufficiency The differences in prognosis as well as in management between the cases of acute and chronic cor pulmonale have been clearly set forth in Chapter 15

Measurements of respiratory function, illustrated in Chapter 17 by Meneely and Calloway, include techniques of differentiating between obstructive and restrictive ventilatory insufficiency. In addition to the tests described in this chapter, the quantative difference between the pulmonary ventilation breathing air and 100 per cent oxygen, as well as breathing air in the head-down position, has been emphasized in the chapters from our clinic as procedures which reveal alterations that are specifically applicable to most patients with pulmonary emphysema. In cases in which the arterial oxygen saturation is normal or nearly normal, hyperventilation is produced by slight or even latent hypoxia, manifested by the prompt decrease in ventilation when a pure oxygen atmosphere is inhaled It would appear that the majority of these patients maintain a heightened minute volume of breathing with

the result that the arterial oxygen saturation is normal or nearly normal.

When a decrease in pulmonary ventilation is obtained by breathing 100 per cent oxygen, retention of CO_2 takes place promptly. However, the diminution in ventilation which results from shifting the patient from the sitting erect to the head-down position is accompanied by both more efficient exchange of oxygen as well as CO_2 due to redistribution of air to better functioning lung parenchyma, notably the hilum. Even with a decrease in ventilation of the order of 20 per cent to 30 per cent, CO_2 is efficiently eliminated; in other words, an increased exchange of both O_2 and CO_2 with a lower pulmonary ventilation takes place when the thorax is tilted headward during the inhalation of air.

Trapping of air may be observed on successive vital capacities in cases with pulmonary emphysema, as pointed out by Meneely, but this response may also be simply demonstrated, even with a portable McKesson Vital Capacity Apparatus, by contrasting the vital capacity produced in a gradual expiration with a fast or forceful expiration. This fast expiration should not be termed a vital capacity since the latter term is reserved, by definition, to the maximum amount of air that can be expelled following a deep inspiration. The so-called "timed" vital capacity is more accurately defined as a timed fast expiration. In the studies reported from our clinic, the vital capacity could be altered as much as 100 per cent in some cases by the speed at which the patient attempted to blow air out from the lungs.

Premature bronchial closure takes place when lung volume is quickly reduced. Since, in the normal individual the fast expiration and vital capacity measurements are the same, the differences that are obtained in pulmonary emphysema may be employed as a diagnostic test as well as a baseline for therapeutic procedures. Although the pneumotachygraph give more accurate figures of velocity of air movement, the high speed drum has long been used for a similar purpose. In 1938 we reported an increase in a patient with bronchial asthma and in a patient with pulmonary emphysema of the expiratory air flow rate after bronchodilators, from

265 to 464 cc. in the former and from 88 to 132 cc. of air per minute in the latter

It should also be mentioned that although a 100 per cent oxygen concentration is employed as a test for the determination of the ventilation with air and oxygen, high concentrations are not used therapeutically in these cases. A marked decrease in the volume of breathing does not take place with low oxygen concentrations, *i e*, 25 per cent The diminution in ventilation which may occur in the clinical treatment of patients with oxygen therapy is one of the advantages of treatment since a graduated increase in the concentration of oxygen inhaled by the patient does not, with the regimen employed in our clinic, produce an uncompensated respiratory acidosis, as has been emphasized in the preceding chapters

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